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# A TEXTBOOK OF ORGANIC CHEMISTRY

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REVISED BY

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NEW EDITION



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LONDON AND GLASGOW

*Companion Volume*

## Practical Organic Chemistry

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Chemistry in the University College of Wales,  
Aberystwyth. Illustrated.

*Nature*: "Altogether the book is probably the most  
complete among those of home manufacture on the sub-  
ject that has yet appeared."

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## PREFACE TO 1941 EDITION

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It is thirty-three years since the first Revised English Edition of *Bernthsen's Textbook of Organic Chemistry* was published, and during these years this branch of chemistry has made enormous advances. The three most marked directions of this advance have been (1) in the borderland between Physical and Organic Chemistry; (2) in the growth of Biochemistry; (3) in the development of the industrial and manufacturing side.

The modern conception of atomic structure has led to new views on the mechanism of many organic reactions as exemplified in aromatic substitution, tautomerism and co-ordinated compounds. It has also entailed the development of the study of such physical properties as dipole moments, lengths of links and X-ray structure.

The study of Biochemistry has entailed a closer study of fermentations, enzyme actions, food metabolism and the functions of vitamins and hormones; also detailed studies of products from the animal and vegetable kingdoms, such as colouring matters, steroids, alkaloids, &c.

Fifty years ago the synthetic dye industry was the chief manufacture based on organic chemistry. This industry has made great strides within the past thirty years, especially as regards azo dyestuffs and vat dyestuffs, but in addition new industries have been developed dealing with synthetic fibres such as rayon, plastics, rubbers, and synthetic drugs, including arsenicals, not to mention oil hardening and fermentation industries such as the manufacture of butyl alcohol and glycerol. The catalytic use of finely divided metals, metallic oxides and salts has also been utilized in the manufacture of numerous compounds.

Attention must also be drawn to the developments in Stereochemistry.

References to all these advances have been incorporated in this Edition, which attempts to give a review of the various

fields covered by "Organic Chemistry"; it does not claim to be in any sense a complete survey. It should be of value to honours students and to those contemplating research in this branch of Chemistry.

General works on Organic Chemistry giving much greater detail are:

1. Meyer and Jacobson, *Lehrbuch der Organischen Chemie*, 2nd Edition (Leipzig).
2. V. Grignard, *Traité de Chimie Organique* (Paris, 1935-39).
3. H. Gilman (Editor), *Organic Chemistry: an advanced treatise* (New York, 1938).
4. Heilbron, *Dictionary of Organic Chemistry* (London, 1934-37).
5. H. Meyer, *Synthese der Kohlenstoff-Verbindungen*.
6. H. Meyer, *Analyse und Konstitutions Ermittlung Organischen Verbindungen* (Vienna, 1938).

In addition there are numerous treatises published in English and dealing with special subjects in this branch of chemistry. References to many of these are given under each chapter.

J. J. SUDBOROUGH.

ERMINGTON, *January, 1941.*

## ABBREVIATIONS

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- A. = Liebig's *Annalen der Chemie*.  
Abs. = *Journal of the Chemical Society*. Abstracts.  
Am. = *American Chemical Journal*.  
Am. J. Pharm. = *American Journal of Pharmacy*.  
Annales = *Annales de Chimie et de Physique*.  
Arch. f. Phys. = *Archiv für Physiologie*.  
Arch. Pharm. = *Archiv der Pharmacie*.  
B. = *Berichte der deutschen chemischen Gesellschaft*.  
B. A. Rep. = *British Association Report*.  
B. bot. Ges. = *Berichte der deutschen botanischen Gesellschaft*.  
Bio. J. = *Biochemical Journal*.  
Bio. Z. = *Biochemische Zeitschrift*.  
Bull. Soc. = *Bulletin de la Société chimique de France*.  
Bull. Soc. Bel. = *Bulletin de la Société chimique de Belgique*.  
Bur. Stand. J. Res. = *Journal of Research of Bureau of Standards*.  
C. and I. = *Chemistry and Industry*.  
C. N. = *Chemical News*.  
C. R. = *Comptes rendus de l'Académie des Sciences*.  
C. W. = *Chemisch Weekblad*.  
C. Z. = *Chemisches Zentral-blatt*.  
C. Zeit. = *Chemiker Zeitung*.  
Can. J. Res. = *Canadian Journal of Research*.  
Chem. Rev. = *Chemical Review*.  
Chem. Rev. Can. Chem. = *Chemical Review of Canadian Chemistry*.  
E. P. = *English Patent*.  
Helv. = *Helvetica Chimica Acta*.  
I. R. World = *India-rubber World*.  
Ind. J. P. = *Indian Journal of Physics*.  
J. A. C. S. = *Journal of the American Chemical Society*.  
J. biol. C. = *Journal of Biological Chemistry*.  
J. C. S. = *Journal of the Chemical Society*. Transactions.  
J. I. E. C. = *Journal of Industrial and Engineering Chemistry*.  
J. I. I. S. = *Journal of the Indian Institute of Science*.  
J. org. = *Journal of Organic Chemistry*.  
J. Pharm. S. J. = *Journal of the Pharmaceutical Society of Japan*.

- J. pr.* = *Journal für praktische Chemie.*  
*J. Ph. Chem.* = *Journal of Physical Chemistry.*  
*J. R. S. A.* = *Journal of the Royal Society of Arts.*  
*J. russ. Soc.* = *Journal of the Physical and Chemical Society of Russia.*  
*J. S. C. I.* = *Journal of the Society of Chemical Industry.*  
*J. S. Dyers* = *Journal of the Society of Dyers and Colourists.*  
*Koll.* = *Kolloid Beihefte.*  
*M.* = *Monatshefte für Chemie.*  
*P.* = *Proceedings of the Chemical Society.*  
*P. Roy. S.* = *Proceedings of the Royal Society.*  
*P. R. S. A.* = *Proceedings of the Royal Society of Arts.*  
*Phil. Mag.* = *Philosophical Magazine.*  
*Phys. Rev.* = *Physical Review.*  
*R. Bio.* = *Review of Biochemistry.*  
*Rec.* = *Recueil des Travaux chimiques des Pays-Bas.*  
*Rep.* = *Annual Reports on the Progress of Chemistry, Chemical Society.*  
*Rep. App.* = *Reports of the Progress of Applied Chemistry. Soc. Chem. Ind.*  
*S. J.* = *Sudborough and James's Practical Organic Chemistry.*  
*Thorpe's Dic.* = *Thorpe's Dictionary of Applied Chemistry.*  
*Trans. Far.* = *Transactions of the Faraday Society.*  
*Trans. I. R. I.* = *Transactions of the Institution of Rubber Industry.*  
*Z. angew.* = *Zeitschrift für angewandte Chemie.*  
*Z. elec.* = *Zeitschrift für Elektrochemie.*  
*Z. phys.* = *Zeitschrift für physikalische Chemie.*  
*Z. physiol.* = *Zeitschrift für physiologische Chemie.*

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*n* = normal.

O-ether = Oxygen ether.

N-ether = Nitrogen ether.

B.-pt. = Boiling-point.

M.-pt. = Melting-point.

*d* = dextro.

*l* = lævo.

*r* = racemic.

*s* = symmetrical.

*i* = inactive.

*R* = alkyl radical.

*Me* = Methyl,  $\text{CH}_3$ .

*Et* = Ethyl,  $\text{C}_2\text{H}_5$ .

*Ph* = Phenyl,  $\text{C}_6\text{H}_5$ .

*o* = ortho.

*m* = meta.

*p* = para.

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# ORGANIC CHEMISTRY

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## INTRODUCTION

Organic Chemistry is the chemistry of the Carbon Compounds. Formerly those compounds which occur in the animal and vegetable worlds were classed under Organic, and those which occur in the mineral world under Inorganic Chemistry, the first to adopt this arrangement having been *Léméry*, in his *Cours de Chimie* (1675). After the recognition of the fact that all organic substances contain carbon, it was thought that the difference between organic and inorganic compounds could be explained by saying that the latter were capable of preparation in the laboratory, but the former only in the organism, under the influence of a particular force, the life force—*vis vitalis*—(*Berzelius*). But this assumption was rendered untenable when *Wöhler* in 1828 synthetically prepared urea,  $\text{CON}_2\text{H}_4$ , a typical secretion of the animal organism, from cyanic acid and ammonia, two compounds which were at that time held to be inorganic; and when, shortly afterwards, the synthesis of acetic acid, by the use of carbon, sulphur, chlorine, water, and zinc, was effected.

Since then so many syntheses of this kind have been achieved as to prove beyond doubt that the same chemical forces act both in the organic and inorganic worlds.

The separation of the two branches, Organic and Inorganic Chemistry, from each other is, however, still retained for convenience sake. In consequence of the great capacity of combining with one another which carbon atoms possess, the number of organic compounds is extraordinarily large, and in order to be in a position to study them, it is necessary to have a knowledge of the other elements, including the metals. The carbon compounds, many of the most important of which contain only carbon and hydrogen, or carbon, hydrogen, and

oxygen, also stand in a closer relationship to each other than do the compounds of the other elements. Partly upon grounds of convenience, carbon itself and some of its principal compounds, such as carbonic acid, which is so widely distributed in the mineral kingdom, are treated of under Inorganic Chemistry.

The expressions "organic" and "organized" substances should not be confused; organized substances, e.g. leaves, nerves and muscles, and also the life-processes which go on in the interior of the organism, are treated of under Physiology and Bio-chemistry.

Of the numerous carbon compounds actually known (some 350,000) relatively few are found in the vegetable or animal kingdom, the large majority are laboratory products—synthetic products. Most of the products dealt with in the major industries, e.g. aniline dyes, synthetic drugs, explosives, synthetic plastics are not found in nature. In the early days the compounds isolated from the vegetable and animal kingdoms were analysed, their molecular weights determined if possible, their reactions studied and structural formulæ allocated and the final process was the confirmation of such formulæ by synthesis in the laboratory, and, in later years, the development of synthetical methods for manufacturing the compounds on the large scale so that in many cases the synthetic products replaced the naturally occurring compounds. Examples of this will be referred to in the case of alizarin and indigo. There are, however, numerous natural products which so far have not been obtained synthetically, e.g. the complex compounds starch and cellulose and the simple compound cane sugar. In the latter case syntheses have been described but are of no practical importance.

The chief sources for the preparation of synthetic products are:

1. Coal, which when subjected to destructive distillation, yields as one of the products coal tar, from which benzene, naphthalene, phenol, anthracene can be isolated, and these are the materials from which dyes, drugs and explosives are manufactured (cf. Chap. LIX and LXV).

2. Crude petroleum, now used as the source for manufacture of halides, alcohols, &c. (Chap. I, A.).

3. Cellulose, used for the manufacture of artificial silk, plastics, explosives, &c.

4. Starch, for alcohol, butyl alcohol, acetone, &c.

## Constituents of the Carbon Compounds

Many organic substances are composed of carbon and hydrogen only, and are then termed hydrocarbons, for instance, ethylene, benzene, petroleum, naphthalene, and oil of turpentine; a vast number consist of carbon, hydrogen, and oxygen, for instance, wood spirit, alcohol, glycerine, aldehyde, oil of bitter almonds, formic acid, acetic acid, stearic acid, tartaric acid, benzoic acid, carbolic acid, tannic acid, and alizarin; many compounds contain carbon, hydrogen, and nitrogen, for instance, prussic acid, aniline, and coniine; as examples of compounds containing carbon, hydrogen, nitrogen, and oxygen, may be taken urea, uric acid, indigo, morphine, and quinine. In addition to these, sulphur, chlorine, bromine, iodine, phosphorus, and, generally speaking, the larger number of the more important elements, are also frequent constituents of the carbon compounds.

## Analysis of Organic Compounds

The methods adopted for the detection and estimation of C, H, N, S, halogens, &c., will be found in any book on Practical Organic Chemistry. Within recent years micro-analytical methods have become common as they require only a few mgs. of material (cf. S. and J., Chap. IV and V).

## The Calculation of the Empirical Formula

The same principle applies as in the case of inorganic compounds, i.e. the percentage numbers found are divided by the atomic weights of the respective elements, the relative proportions of the quotients obtained being expressed in whole numbers. For instance, acetic acid being found to contain 40.11 p.c. carbon, 6.80 p.c. hydrogen, and, consequently, 53.09 p.c. oxygen, the quotients are to each other as  $3.34 : 6.80 : 3.32 = 1 : 2 : 1$ . The simplest analysis-formula of acetic acid would therefore be  $\text{CH}_2\text{O}$ . Sometimes figures are obtained which correspond with equal nearness to different formulæ, between which it is therefore impossible, without further data, to choose.

For instance, a sample of naphthalene yields on analysis 93.70 p.c. carbon and 6.30 p.c. hydrogen; the quotient

proportion here is  $7.81$  to  $6.30 = 1.239 : 1$ , which corresponds equally well with the numbers  $5 : 4$  or  $11 : 9$ . The formula  $C_5H_4$  requires  $93.75$  p.c. carbon and  $6.25$  p.c. hydrogen, and the formula  $C_{11}H_9$ ,  $93.62$  p.c. carbon and  $6.38$  p.c. hydrogen, the deviations from the actual numbers found being in both cases within the limits of experimental error. Therefore other considerations must be taken into account here, in order to decide between the two formulæ.

The formula derived from the results of analyses is termed the **Empirical Formula**, and expresses the simplest numerical relationship between the atoms of the elements present. The actual molecular formula may be a multiple of this, and has to be determined according to special principles.

## Determination of Molecular Weight

### 1. BY CHEMICAL METHODS.

Our chemical formulæ (e.g.  $CH_2O$ ) express not merely a percentage relation, but at the same time the smallest quantity of the compound which is capable of existing as such, i.e. a molecule of it. This molecule is ideally no longer divisible by mechanical means, but only by chemical, and then into its constituent atoms. If the formula  $CH_2O$  were the correct one for acetic acid, then the amount of oxygen (or carbon) contained in a molecule would be indivisible, and that of hydrogen divisible only by 2. Since, however, it has been observed that one-fourth of the total hydrogen in acetic acid is replaceable, e.g. by a metal, with the formation of a salt, it is obvious that the quantity of hydrogen in the molecule must be divisible by 4, and so the formula must contain at least 4 atoms of hydrogen, and must therefore be  $C_2H_4O_2$ , or some multiple of it. This is, in fact, the case. Acetate of silver contains  $64.67$  p.c. silver, and therefore  $35.33$  p.c. of the acetate radical; or, to 1 atom of silver = 108 parts by weight, there are 59 parts by weight of the acid radical. This 59, together with 1 atom of hydrogen = 1, makes the molecular weight of acetic acid 60,  $= 2 \times 30$ ,  $= 2 \times CH_2O$ ,  $= C_2H_4O_2$ .

This is a determination of molecular weight by **chemical means**. Such determinations are carried out in the case of acids generally by means of their silver salts; these are usually normal salts, are easy to purify, are almost always free from water of crystallization, and are readily analysed. It is,

however, *absolutely necessary* to know whether the acid is mono- or polybasic. In the case of a di-, tri-, &c., basic acid, the above calculation must be made with reference to 2, 3, &c., atoms of silver, whereas acetic acid—being monobasic—contains only one replaceable atom of hydrogen, which is therefore exchanged for one atom of silver. Consequently, its formula cannot be a multiple of  $C_2H_4O_2$ .

In the determination of the molecular weights of **Bases**, their platinichlorides are similarly made use of, these being almost always constituted on the type of ammonium platinichloride:  $(NH_3)_2H_2PtCl_6$ : i.e. they contain two molecules of a mono-acid base such as ammonia combined with one atom of platinum.

To determine the molecular weights of **Neutral Compounds**, derivatives must be prepared and examined for the proportion of the total hydrogen which is replaceable, e.g. by chlorine. For example, by the action of chlorine upon naphthalene, there is first formed the substance monochloronaphthalene, which contains 73.8 per cent C, 4.3 per cent H, and 21.9 per cent Cl, these numbers giving the formula  $C_{10}H_7Cl$ . In the same way benzene yields the compound  $C_6H_5Cl$ . In both these cases the halogen acts by replacing hydrogen, and at least one atom of the latter in the molecule must be replaced, since fractions of an atom are necessarily out of the question. If, then, the compound obtained has the formula  $C_{10}H_7Cl$ , it follows that  $\frac{1}{8}$  of the H present has been replaced by Cl, and there must consequently be 8,  $8 \times 2$ , or  $8 \times 3$ , &c., atoms of hydrogen in the compound, and likewise 10 atoms, or some multiple of 10, of carbon. But a multiple of 8 or 10 may be rejected, since no compounds have been observed which would indicate the replacement of  $\frac{1}{16}$  of the total hydrogen. This leads to the formula  $C_{10}H_8$  for naphthalene, the other possible formula got by analysis, viz.  $C_{11}H_9$  (see p. 4), being now untenable. In a similar way the formula of benzene is found to be  $C_6H_6$ .

## 2. BY PHYSICAL METHODS.

The commoner methods used are:

1. Vapour density method.
2. Cryoscopic method.
2. Ebullioscopic method.
4. Vapour pressure method (for details cf. S. J., Chap. VIII).



## Polymerism and Isomerism

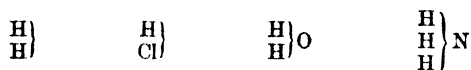
The determination of molecular weight is of the first importance, because different substances very frequently have the same percentage composition and therefore the same empirical formula, and yet are totally distinct from one another. This difference is often due to differences in the complexities of the molecules. Thus formic aldehyde,  $\text{CH}_2\text{O}$ ; acetic acid,  $\text{C}_2\text{H}_4\text{O}_2$ ; lactic acid,  $\text{C}_3\text{H}_6\text{O}_3$ ; and grape-sugar,  $\text{C}_6\text{H}_{12}\text{O}_6$ , have all the same percentage composition; as have also ethylene,  $\text{C}_2\text{H}_4$ ; propylene,  $\text{C}_3\text{H}_6$ ; and butylene,  $\text{C}_4\text{H}_8$ . Compounds standing in such relation to each other are termed **polymers**. Very frequently, however, substances which are totally distinct from each other possess both the same percentage composition and the same molecular weight; that is to say, these compounds are made up not only of the same elements, but also of an equal number of atoms of these elements; such substances are termed **isomers** or **metamers**. (See Ethers.) Thus, for instance, common alcohol and methyl ether, the latter of which is obtained by heating methyl alcohol with sulphuric acid, have one and the same molecular formula,  $\text{C}_2\text{H}_6\text{O}$ .

The striking phenomenon of isomerism is most readily explicable on the assumption that for the molecule of each compound there is a definite arrangement of the atoms, and that this arrangement or grouping is different in the molecules of the two isomerides. This difference in grouping may be considered as being due to a difference in the linking powers of the atoms, as is indicated by the dissimilar chemical behaviour of isomers, and explained by the theory of valency.

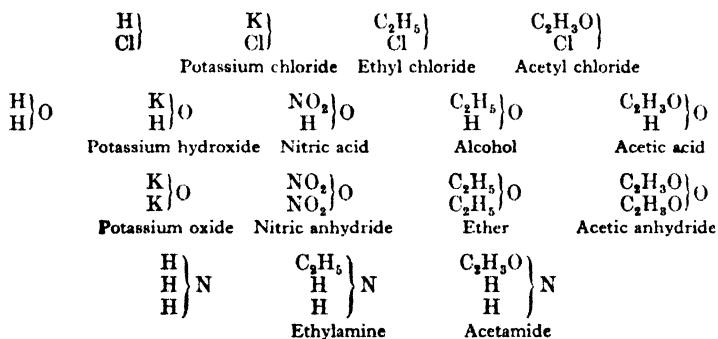
## Chemical Theories; the Theory of Valency

After the fall of the Electro-Chemical theory, unitary formulæ—in contradistinction to the earlier dualistic formulæ—were much used; thus alcohol had the formula  $\text{C}_4\text{H}_6\text{O}_2$  (using the old equivalent weights). The necessity for comparing substances of complicated composition with simpler ones, taken as "Types", had already repeatedly led to the propounding of new theories for representing the constitution of organic compounds, e.g. the older Type theory (*Dumas*), and the Nucleus theory (*Laurent*).

These obtained a firmer basis through *Gerhardt's Theory of Types*, which received support more especially from the discovery of ethylamine and other ammonia bases (*Wurtz*, 1849, and *Hofmann*, 1849, 1850), the proper interpretation of the formulæ of the ethers (*Williamson*, 1850), and the discovery of the acid anhydrides (*Gerhardt*, 1851). All compounds, inorganic as well as organic, were in this way compared with simpler inorganic substances taken as "**Types**", of which *Gerhardt* named four, viz.:



The first two of these really belong to the same type. Thus the following formulæ were arrived at:



&c. &c. Organic compounds could thus, like inorganic, be referred to inorganic types by assuming in them the presence of Radicals (e.g. ethyl,  $\text{C}_2\text{H}_5$ ; acetyl,  $\text{C}_2\text{H}_3\text{O}$ , &c.), i.e. of groups of atoms which play a part analogous to that of an atom of an element, and which can be transferred by double decomposition from one compound to another. Thus ethyl chloride,  $\text{C}_2\text{H}_5\text{Cl}$ ; alcohol,  $\text{C}_2\text{H}_5\text{O}$ ; ethylamine,  $\text{C}_2\text{H}_7\text{N}$ ; ether,  $\text{C}_4\text{H}_{10}\text{O}$ ; &c., were represented as containing the same radical  $\text{C}_2\text{H}_5$ , ethyl, and the close relationship existing between these compounds now found expression in the type formulæ.

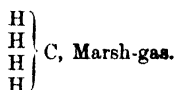
Sulphuric acid,  $\text{H}_2\text{SO}_4$ , was derived from the double water type, thus:



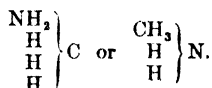
and chloroform,  $\text{CHCl}_3$ , and glycerine,  $\text{C}_3\text{H}_5\text{O}_3$ , from the triple hydrochloric acid and water types:



the assumption being made that the radicals  $(\text{C}_2\text{H}_5)'$ ,  $(\text{SO}_2)''$ ,  $(\text{CH})'''$ , and  $(\text{C}_3\text{H}_5)'''$  could replace a number of hydrogen atoms corresponding with the number of accents (') marked upon them, i.e. that they were monatomic, diatomic, &c. To the above three types *Kekulé* afterwards added a fourth, of especial importance as regards the carbon compounds, viz.:



It was then found that many compounds could be referred equally well to one or another of these types, methylamine, for instance, either to  $\text{CH}_4$  or to  $\text{NH}_3$ , thus:



The assumption, already mentioned, of the atomic groups (radicals) which in these types replaced hydrogen, led further to more exact investigations of the chemical value, i.e. the replaceable value, of those groups as compared with that of hydrogen. In this way chemists learnt to distinguish between uni-, bi-, ter-, &c., valent groups, and, generally speaking, to pay more attention to equivalent proportions.

As the outcome of his researches upon organo-metallic compounds, *Frankland* formulated in 1852 (A., **85**, 368) the law that the elements nitrogen, phosphorus, arsenic, and antimony tend to form compounds which contain three or five equivalents of other elements.

*Kekulé* then, in 1857-58 (A., **104**, 129; **106**, 129), proceeded to show that a more profound idea (the "Type idea") lay at the root of the types themselves, viz. that there are uni-, bi-, tri-, and quadrivalent, &c., elements, which possess a corresponding replacing or combining value as regards hydrogen; and that hydrogen is therefore univalent, oxygen bivalent, nitrogen trivalent, carbon quadrivalent, and so on.

With the introduction of the  $\text{CH}_4$  type by *Kekulé*, and the

establishment of the quadrivalent nature of the carbon atom accompanying this, were connected the endeavours of *Kolbe* to derive the constitution of organic compounds from carbonic acid (according to *Kolbe*,  $C_2O_4$ ,  $C = 6$ ,  $O = 8$ ), by the exchange of oxygen for organic radicals (A., 113, 293); see also, for further details, *Kopp's* "Entwicklung der Chemie in der neueren Zeit" (Oldenbourg, Munich, 1873), and *E. V. Meyer's* "History of Chemistry" (Macmillan, 1891), *Schorlemmer's* "Rise and Development of Organic Chemistry" (Macmillan).

The question of the valency of elements, a point which it is often difficult to decide in inorganic chemistry, is infinitely easier of determination in the case of the carbon compounds, because the carbon atom is **quadrivalent** towards hydrogen as well as towards chlorine and oxygen. Since the atom of hydrogen, as the unit of valency, is univalent, and, further, since the bivalence of the oxygen atom cannot reasonably be doubted, the valency of the three "organic" elements hydrogen, oxygen, and carbon may be considered as resting upon a sure basis, as may also the conclusions drawn therefrom, and this all the more since the most important carbon compounds are made up of those three elements.

The above are the normal valencies of H, O and C, but oxygen can be quadrivalent in the oxonium salts (Chap. XLIII, A.), and carbon bi- and trivalent (Chap. LII, B.).

### Explanation of Isomerism; Determination of the Constitution of Organic Compounds

The phenomenon known as isomerism is elucidated to a great extent by the theory of valency. If two substances have the same molecular formula, i.e. both contain the same elements and the same number of atoms of the respective elements in their molecules, then the obvious conclusion to be drawn is that in the two molecules the atoms are differently arranged. The methods adopted in determining the manner in which the atoms are linked together, or, as it is called, the determination of the chemical constitution of the compound, is usually based on the following points: (a) The respective valencies of the atoms constituting the molecule. A compound

$C_2H_6$  must have the structural formula  $\begin{array}{c} H & & H \\ & \diagdown & / \\ H & - C - C - & H \\ & / & \diagdown \\ H & & H \end{array}$ , or, as

it is often more shortly written,  $\text{CH}_3\cdot\text{CH}_3$ , if each atom of carbon is to be represented as quadrivalent, and each hydrogen atom as univalent. Similarly the compound  $\text{CH}_4\text{O}$  must be

represented as  $\begin{array}{c} \text{H} & & \text{H} \\ & \diagdown & / \\ & \text{C} & \\ & / & \diagdown \\ \text{H} & & \text{O}-\text{H} \end{array}$ , or  $\text{CH}_3\cdot\text{OH}$  if the carbon atom

is quadrivalent, the oxygen atom bivalent, and the hydrogen atoms univalent. (b) A study of the more important methods of formation and of the chemical reactions in which the compound in question can take part. To select as an example ethyl alcohol,  $\text{C}_2\text{H}_6\text{O}$ . If we start from ethane,  $\text{CH}_3\cdot\text{CH}_3$ , and by the action of chlorine replace one of the hydrogen atoms by a chlorine atom, the compound  $\text{CH}_3\cdot\text{CH}_2\text{Cl}$  is formed. When this is boiled with dilute alkalis ( $\text{KOH}$ ), it gives potassium chloride and ethyl alcohol,  $\text{C}_2\text{H}_5\text{Cl} + \text{KOH} = \text{C}_2\text{H}_6\text{O} + \text{KCl}$ . From this it is obvious that the univalent chlorine atom becomes replaced by an atom of oxygen and an atom of hydrogen. This can be readily understood if we assume that these two atoms enter in the form of the univalent hydroxyl group,  $-\text{O}-\text{H}$ , and the *constitutional*

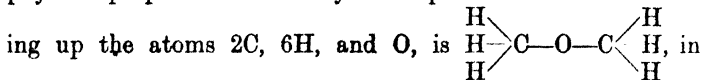
*formula* for ethyl alcohol would then be  $\begin{array}{c} \text{H} & & & \text{H} \\ & \diagdown & & / \\ & \text{C} & - & \text{C} \\ & / & & \diagdown \\ \text{H} & & & \text{O}-\text{H} \end{array}$  or

$\text{CH}_3\cdot\text{CH}_2\cdot\text{OH}$ . This formula is further supported by a study of most of the chemical reactions in which ethyl alcohol can take part. It can react with metallic sodium, yielding a compound, sodium ethoxide,  $\text{C}_2\text{H}_5\text{NaO}$ ; however much sodium is employed, only one of the six hydrogen atoms present in the alcohol molecule can be replaced by sodium, and this atom is presumably the one differently situated from the remaining five, namely, the one attached to oxygen. The presence of the hydroxyl,  $-\text{O}-\text{H}$ , group is further confirmed by the action of hydrogen chloride or of phosphorus trichloride on the alcohol, when an atom of chlorine takes the place of the  $\cdot\text{OH}$  group.



Isomeric with ethyl alcohol is the substance known as dimethyl ether. Although it has the same molecular formula, it differs altogether from ethyl alcohol in its chemical and

physical properties. The only other possible method of linking up the atoms 2C, 6H, and O, is

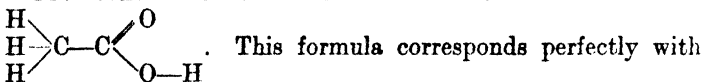


in which the two carbon atoms are not directly united to one another, and in which the six hydrogen atoms are all similarly situated. The chemical reactions of dimethyl ether are in perfect harmony with this constitutional formula. It does not react with metallic sodium, and hence presumably does not contain an OH group. When acted upon by hydriodic acid, under suitable conditions, the molecule is ruptured, as represented by the following equation:



Similarly, whenever the oxygen atom is removed a rupture of the molecule occurs, and the two carbon atoms in the molecule become separated.

The constitutional formula for acetic acid is written



This formula corresponds perfectly with the chemical behaviour of acetic acid and explains the following facts: (a) that one of the hydrogen atoms of the acid possesses properties different from those of the three others, the first-named being easily replaceable by metallic radicals; (b) that the two oxygen atoms behave differently, not being equally readily exchangeable for other radicals; (c) that different functions appertain to the two carbon atoms, so that one of them—being already joined to two atoms of oxygen—easily give rise to carbonic acid, while the other—connected as it is with three atoms of hydrogen—readily passes into methane or methyl compounds.

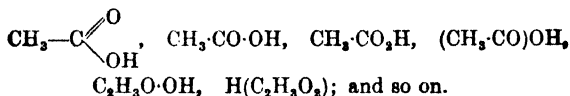
On account of the innumerable cases of isomerism which have been observed, simple molecular formulæ alone are in most cases insufficient for the discrimination of organic compounds; it generally requires the constitutional formulæ to give a clear idea of their behaviour and of their relations to other substances. Careful study has made it possible within the last few decades to find out the mode in which the atoms are combined in the molecules of most organic compounds, and from this to deduce new methods for their preparation. The constitutional formulæ thus arrived at are sometimes simple,

sometimes, however, complicated, as, for instance, in the cases of citric acid and grape-sugar (Chap. XI, B., and XIV, A.).

### Rational Formulæ

Great latitude is permissible as regards the mode of writing constitutional formulæ, according to the particular points which it is desired to emphasize. A formula on paper is not as a rule intended to represent the symmetrical or spatial arrangement of the atoms in a compound.

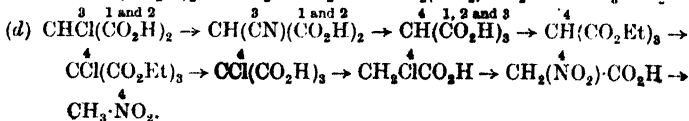
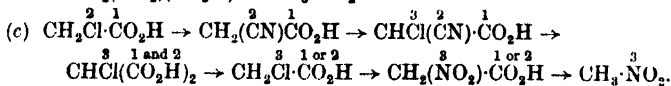
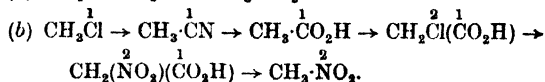
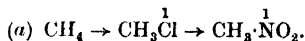
A shortened constitutional formula, which indicates more chemical relations than an empirical one does, is called a *rational* formula; e.g.  $C_2H_5OH$ , alcohol;  $(CH_3)_2O$ , methyl ether; acetic acid,



### Types of Carbon Compounds

The following generalizations have been reached as the result of the study of carbon compounds:

1. The carbon atom is normally quadrivalent.
2. The four valencies in a compound like  $CH_4$  or  $CCl_4$  are all equal. A compound  $CH_3X$  exists in only one form; no isomeride is known. The equality in the case of  $CH_4$  was proved by *Henry*, who replaced each of the 4 H atoms (1, 2, 3 and 4) by  $NO_2$  and obtaining only one compound,  $CH_3 \cdot NO_2$ , whichever H was replaced. The method is outlined in the following 4 series of reactions:



The same product is obtained in all 4 cases. The reactions involved above are replacement of H by Cl by direct chlorination, replacement of Cl by CN or by  $\text{NO}_2$  by action of alcoholic KCN or  $\text{KNO}_2$ ; hydrolysis of CN to  $\text{CO}_2\text{H}$  by alkali, elimination of  $\text{CO}_2$  from  $\text{CO}_2\text{H}$  by heating.

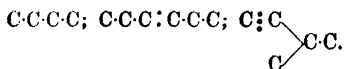
3. The four groups attached to the central carbon are arranged spatially and not in a single plane (Chap. VI, Valeric Acid).

4. The groups attached to the central carbon atom cannot be *readily* interchanged. That such changes can occur is proved by the racemization of optically active compounds.

5. Unless direct proof to the contrary is available it is concluded that in reactions such as those mentioned in section 2, the group introduced takes the place of the group replaced. (See Chap. XXXVIII, Molecular Rearrangement).

6. Several carbon atoms can be connected together by either one, two, or three valencies (see p. 51):  $\text{C}\cdot\text{C}$ ,  $\text{C}:\text{C}$ ,  $\text{C}\equiv\text{C}$ .

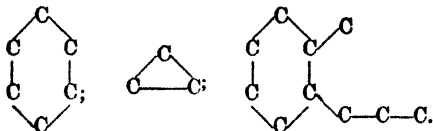
7. Similarly three or more carbon atoms may be united, forming in this way the so-called "carbon chains" (see p. 31), thus:



The number of the atoms so linked together may be very large—in some cases probably several hundreds.

8. These carbon atoms form either open or ring-shaped closed chains.

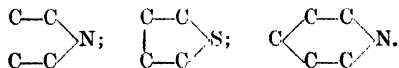
*Open chains* are those which have separate constituent atoms at either end, as in (7). In *closed chains* or *rings*, on the contrary, the first and last constituent atoms are linked together (although there may at the same time be subsidiary branches from them), thus:



9. The atoms of other elements, with the exception, of course, of univalent ones, may likewise take part in the



formation of such chains, both open and closed; for example:



The above figures (the hexagon, &c.), which are made use of to represent such chains or rings, are merely meant to be pictorial and not geometrical; the question of the spatial arrangement of atoms in compounds is dealt with later. (See Active Valeric Acid, Chap. VI, A.)

## Atomic Structure, Valency and Types of Linkings

The following is a list of nine elements of low atomic weight from which the great mass of carbon compounds are derived.

	At. Wt.	At. No.	Arrangement of Electrons in Shells
H	1	1	1
C	12	6	2.4
N	14	7	2.5
O	16	8	2.6
Na	23	11	2.8.1
Mg	24	12	2.8.2
P	31	15	2.8.5
S	32	16	2.8.6
Cl	35.5	17	2.8.7.

The third column gives the atomic number of the element in the order of increasing atomic weight and represents the number of electrons surrounding the central positively charged nucleus. These extra-nuclear electrons are arranged in shells, outer, intermediate and inner, and it is the number of electrons in the outer or valence shell, i.e. the figure to the extreme right in column 4 which decides the valency and type of compounds the element will form.

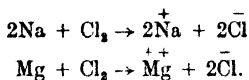
When these electron shells are compared with those of the inert gases of low atomic weight, viz. helium, neon and argon,

He	4	2	2
Ne	20	10	2.8
Ar	40	18	2.8.8

it is clear that the difference between the chemically active elements and the inert gases lies in the number of electrons in

the outer shell. Not one of the active elements has the stable arrangement 2 (helium) or 8 (Ne and A) in the outer sphere. The chemical reactions in which the other elements take part consist in absorbing or discarding electrons so that in the compounds formed the outer shell of each atom has 8 electrons. This may be brought about by the different types of links.

1. **Electro-valency links** which are those met with in ionizable compounds. In the combination of sodium and chlorine the Na gives up its one electron in the outer sphere to the chlorine, then both atoms have outer shells of 8 electrons, but by losing an electron the Na becomes positively charged  $\text{Na}^+$  and the Cl by receiving an extra electron becomes negatively charged  $\text{Cl}^-$ .



In the latter case the Mg loses 2 electrons, one to each chlorine atom and here again  $\text{Mg}^{++}$  and  $\text{Cl}^-$  have the stable octet of electrons. In these compounds, electrolytes for all practical purposes, the ions react as individual molecules and are held together by electrostatic forces only.

### *Characteristics of Electrovalent Compounds.*

(a) X-ray diffraction methods applied to crystals show that in the solid salts the molecules, e.g. NaCl, do not exist, but that the crystals are built up of two interpenetrable lattices due to the individual atoms or ions  $\text{Na}^+$  and  $\text{Cl}^-$ .

(b) In suitable solvents or in the molten state the compounds exhibit a high degree of electric conductance, as the restraining forces of the crystal lattice are no longer effective.

(c) Relatively high boiling-points.

(d) Soluble in associated solvents, particularly those containing hydroxyl groups.

2. **Covalency links** are those commonly met with in carbon compounds. Simple examples are the chlorine molecule and the methane molecule. According to *G. N. Lewis* two atoms can unite in such a manner that each shares an electron of its outer shell with the other, and such shared electrons count

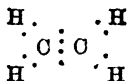
towards the outer shell of each and in this way each atom attains the stable octet structure. Thus Cl has 7 electrons in the outer shell, but in the molecule,  $\text{Cl}_2$ , each atom shares one electron with the other and each shared electron counts, so that each of the combined atoms has the stable shell of 8 electrons (6 unshared and 2 shared). Similarly, with methane,



the carbon has 4, and each hydrogen 1 electron in their outer shells, but by each H sharing an electron with C and C sharing one of its four with each H, the H attains the stable helium structure and the carbon the stable octet of neon.

The elements in such covalency union are usually, although not always, electro-negative, and the links are, as a rule, not readily ionizable. In this type of union the sharing of electrons is always in pairs—one electron coming from each of the two atoms involved—and is the common type met with between C and C, C and H, H and O, C and N, C and O.

In later chapters many examples of compounds in which carbon atoms are linked by two, or even three, bonds are described (Chap. I, B. and C.). In the majority of cases these bonds are covalency links, and *each* of the 2 or 3 bonds is formed by the sharing of two electrons—one from each of the two atoms, e.g.:  $\text{C}_2\text{H}_4$ , ethylene,



All compounds with covalent links can be depicted by such formulæ, each dot representing an electron in the outer shell of an element, and if any such electrons are unshared they can also be represented, e.g.  $\text{NH}_3$ :



indicating that each H is attached to N by a covalent link,

but that the N still has two unshared electrons (a lone pair). With more complex compounds this method of representation becomes cumbersome, and the English method of represent-

ing a covalent link is by a straight line so that

$$\begin{array}{c} \text{H} & & \text{H} \\ & \diagdown & / \\ & \text{C}=\text{C} \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array}$$

can be used to represent the structure of ethylene on the covalent link basis, and similarly for all other compounds with covalent links; if lone pairs of electrons (unshared electrons) are present each pair can be represented by a straight

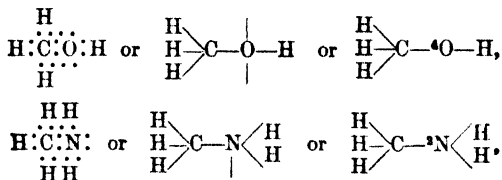
line; thus ammonia is written  $\text{—N} \begin{array}{l} \diagup \text{H} \\ \diagdown \text{H} \\ \text{H} \end{array}$ , and it is seen that each

hydrogen has the stable duplet (of helium) and the nitrogen the stable octet (of neon).

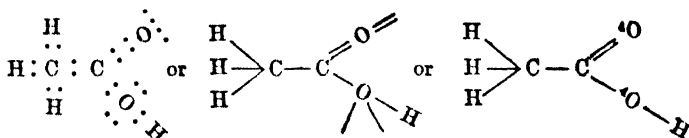
Another method is to indicate the unshared electrons of the outer shell by a small number at the upper left-hand of

the symbol, e.g.  $^3\text{N} \begin{array}{l} \diagup \text{H} \\ \diagdown \text{H} \\ \text{H} \end{array}$

The oxygen molecule can be represented as  $=\text{O}=\text{O}=$  or  $^4\text{O}=\text{O}$  and the nitrogen molecule as  $\text{—N}\equiv\text{N—}$  or  $^3\text{N}\equiv\text{N}$ ; the compounds  $\text{CH}_3\cdot\text{OH}$  and  $\text{CH}_3\cdot\text{NH}_2$  as



and  $\text{CH}_3\cdot\text{CO}\cdot\text{OH}$  as



No compounds containing two atoms united by 4 covalent links are known.

*Characteristics of Covalent Compounds.*

(a) Usually built up of electro-negative elements, i.e. a metal is rarely attached to another atom by a covalent link.

(b) Usually soluble in non-associated solvents with low dielectric constants.

(c) The union implies a definite directional bond and hence stereo-isomerism is possible, thus C and H in  $\text{CH}_4$  have four shared pairs of electrons, and the most symmetrical arrangement is one pair at each corner of a regular tetrahedron and hence the three-dimensional arrangement of carbon compounds.

(d) Relatively volatile.

According to *Lewis* there is not a hard and fast line of division between the electrovalent and the covalent link. In the ideal covalent link the sharing of the two electrons between the two atoms is equal, and hence no disturbance of the electric distribution occurs; this is true of  $\text{H}_3\text{C}-\text{CH}_3$ , where there is no reason for one carbon atom to have a larger share in the distribution than another as the molecule is symmetrical. In other cases there must be unequal sharing due to the influence of different groups attached to the two atoms or to the atoms themselves being different, e.g. C and N, and finally a state is reached when an electron passes from one atom to the other and an electrovalent link results. Unequal sharing leads to uneven electrical distribution and dipole moments are set up (Chap. LXXI, G.).

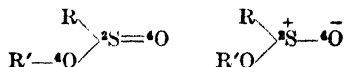
**3. Semipolar links** (*Lowry*).

It has been stated (p. 16) that in most cases where two carbon atoms are doubly linked as in the olefines the union is by means of two covalent links and in many cases double bonds between C and O, C and S, C and N consist of two covalent links. In some cases, however, the union is more complex and consists in one covalent link and one electro-

valent link and is represented as  $\begin{array}{c} \diagup \quad \diagdown \\ \text{C}^+ - \bar{\text{C}}^- \\ \diagdown \quad \diagup \end{array}$ ,  $\begin{array}{c} \diagup \quad \diagdown \\ \text{S}^+ - \bar{\text{O}}^- \\ \diagdown \quad \diagup \end{array}$ .

Semipolar links in the case of C—C bonds or C—O bonds would be unstable as the  $\begin{array}{c} \diagup \quad \diagdown \\ \text{C}^+ - \bar{\text{C}}^- \\ \diagdown \quad \diagup \end{array}$  or  $\begin{array}{c} \diagup \quad \diagdown \\ \text{C}^+ - \bar{\text{O}}^- \\ \diagdown \quad \diagup \end{array}$  entails C atoms with an outer sheath of six electrons whereas the ordinary dicovalent formulæ give the stable octet for the C and O atoms involved. With the S=O link, however, as typified in

the sulphuric esters, the double bond formula should be the unstable form as it entails an S atom with an outer sheath of 10 electrons whereas the semipolar formula provides the S atom with the stable octet.



Additional evidence for the semipolar formula is available (cf. Chap. L, E.).

It is clear that the introduction of the electrovalency in place of one of the covalencies disturbs the electric balance of the molecule; the molecule as a whole remains electrically neutral, but the distribution of the positive and negative charges is clearly not uniform, and hence dipole moments will arise (cf. Chap. LXXI, G.).

From a stereochemical standpoint the semipolar link is equivalent to a single covalent link, and hence the loss of rotation due to a double bond no longer holds.

#### 4. Co-ordinate links (*Sidgwick*).

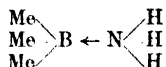
On comparing the electronic formulæ of a number of simple compounds, it is found that there is a group in which one of the atoms, although having a stable octet, has not utilized all its available electrons; a typical example is ammonia  $\text{NH}_3$ ,



in which the nitrogen atom shell has a pair of lone electrons. A second group exists, e.g.  $\text{BMe}_3^*$  in which there is an atom in which all the available electrons are engaged, but which has not a full octet. It is clear that the nitrogen atom cannot form any more covalent links if it is not to exceed the octet, but it has two electrons available; on the other hand, the B atom has no electrons available for forming more covalent links, but is two short of the stable octet. A union, involving two electrons, between the N and B atoms could take place if both electrons were derived from the nitrogen and then both N and B would have the stable octet. Six of the links in the compound would be covalent links, viz.  $3\text{N}-\text{H}$  and  $3\text{Me}-\text{B}$ , but the 7th link, viz. between B and

\* Me represents methyl group  $-\text{CH}_3$ .

N, would be of a different type formed by two electrons both derived from the same atom (N) which is termed the donor; the link is called a *Co-ordinate link*, and is denoted by  $\rightarrow$ . The arrow points from the donor to the acceptor, and the compound



is termed a co-ordinate compound.

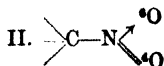
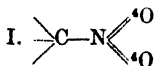
Compounds with such links are very common, and many types are discussed in Chap. XLVI.

It is clear that the C atom in a compound like methane can act as neither donor nor acceptor as its 4 electrons are all utilized and it has the complete octet.

Typical donors are (i) 3 covalent N in ammonia and amines; (ii) 2 covalent O and S in water, alcohols, ethers, &c.; (iii) F in hydrogen fluoride and 1 covalent iodine. Typical

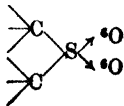
acceptors are (i) Proton ( $\text{H}^+$ ) which can unite with water and other oxygen compounds to give oxonium salts, with ammonia to give ammonium salts; (ii) 3 covalent B and its alkyl and halide derivatives; (iii) 2 covalent Mg and Zn and their alkyl derivatives.

It is to be noted that the stable octet is never exceeded in the case of elements of the first period. Where a covalent structure for a compound would produce a number greater than 8 it is usual to represent, where possible, certain links as co-ordinate links, e.g. the nitro group attached to carbon:



According to formula I, the C and O atoms would have a stable octet (each O having 2 pairs of unshared electrons), but the N would have an outer shell of 10. Writing this with a co-ordinate structure II, all atoms C, N and O have the stable octet.

Similarly,  $(\text{CH}_3)_2\text{SO}_2$  is written:



The presence of co-ordinate links always disturbs the electric balance and produces compounds with pronounced dipole moments.

Co-ordinate links account for the association of many organic oxygen compounds and for the physical properties of certain substituted phenols and  $\beta$ -ketonic esters (Chap. XLVI, B.).

For all practical purposes the semipolar double link and the co-ordinate link are identical.

1. They do not function between carbon atoms, but usually between O and N or S and N or O and metal.

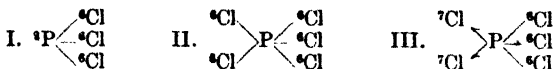
2. Their presence is always accompanied by electric disturbances (polar moments). The limit is reached when the one element has a distinct negative charge of one electron, e.g. the acceptor sharing equally the two electrons provided by the donor, and the other atom a corresponding positive charge.

(3) From the stereochemical point of view they are equivalent to a covalent link.

5. Singlet link (*Pauling, 1931*).

A union of two atoms by means of a single electron first suggested by *Pauling* has been adopted by *Sugden* from a study of certain *parachors* (Chap. LXXI, H2) and also to obviate the necessity of increasing the outer sheath of electrons of some simpler elements beyond the stable 8.

Thus  $\text{PCl}_3$  unites with  $\text{Cl}_2$  given  $\text{PCl}_5$ . If the two extra chlorines become attached by



covalencies as in II, then the P atom has an outer sheath of 10 electrons, whereas if the union occurs by means of two singlet links each derived from phosphorus and denoted by  $\rightarrow$ , a structure in which the P atom has a stable octet is obtained.

Many chemists do not accept this view, and prefer an increase in the outer sheath of simple elements beyond 8.

The hydrogen molecule  $\text{H}_2^+$  which occurs in a vacuum tube, involves a singlet link as there is only one electron to unite the two hydrogens.

*Samuel* (1927) does not accept either singlet or co-ordinate links. He considers that in all cases there is a sharing of



electrons in pairs, but that the degree of sharing varies considerably in different types of compounds, in moist HCl it is practically nil, but in dry HCl it is large, and such unsymmetrical molecules develop dipole moments. Symmetrical molecules, e.g.  $\text{Cl}_2$ , are non-polar. These are the extreme types, and all compounds fall between these extremes.

## Homology

In the study of carbon compounds it is customary to group together all the compounds with similar chemical structure and similar chemical properties, and to arrange the members of such a group, or *homologous series* as it is termed, according to the order of their molecular complexity, i.e. according to the number of carbon atoms contained in the molecule.

For example:

Paraffins		Fatty acids	
$\text{CH}_4$	methane ..	..	$\text{CH}_2\text{O}_2$ formic
$\text{C}_2\text{H}_6$	ethane ..	..	$\text{C}_2\text{H}_4\text{O}_2$ acetic
$\text{C}_3\text{H}_8$	propane ..	..	$\text{C}_3\text{H}_6\text{O}_2$ propionic
$\text{C}_4\text{H}_{10}$	butane ..	..	$\text{C}_4\text{H}_8\text{O}_2$ butyric

It is found that in any such *homologous series* a number of generalizations can be drawn. Some of the more important of these are:

1. For each homologous series a *general formula* can be written which will represent the composition of all the members of the series; for example, the general formula for the paraffins is  $\text{C}_n\text{H}_{2n+2}$ , and for the saturated fatty acids  $\text{C}_n\text{H}_{2n}\text{O}_2$ .

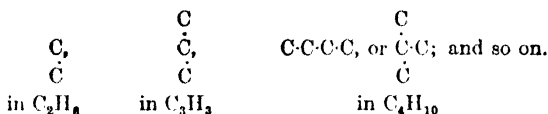
2. If any particular member in a series is selected, it is found to differ in composition from the member immediately preceding, and also from the one immediately succeeding, it by a definite amount, namely,  $\text{CH}_2$ . Or, expressed in other words, any member of the series may be regarded as derived from the member immediately preceding it by the introduction of a methyl group,  $\cdot\text{CH}_3$ , for an atom of hydrogen. It follows, therefore, that all the members of the paraffin series may be regarded as derived from  $\text{CH}_4$  by the addition of a given number of  $\text{CH}_2$  groups, and the general formula is for this series  $\text{CH}_4 + x\text{CH}_2$ , or more simply  $\text{C}_n\text{H}_{2n+2}$ .

3. The chemical properties of the different members of the series vary but slightly, so that a description of the chemical

properties of any one member may be taken, as a rule, to apply to the other members.

4. In studying the physical properties, well-marked gradations are observed as the number of carbon atoms increases. In the case of liquids, the boiling-point is found to rise as the complexity of the molecule increases. In certain series, e.g. the paraffins, the first few members are gases, then follow liquids with gradually increasing boiling-points, and ultimately solids with extremely high boiling-points. Other physical data, such as melting-point, specific gravity, solubility, &c., are affected in very much the same manner.

In the paraffin series the grouping of the carbon atoms must be conditioned by themselves, since hydrogen, as a univalent element, cannot be the cause of it. In all the higher hydrocarbons the carbon atoms are therefore combined together in the form of a chain, as shown in the following graphical representations:



The different methods of grouping give rise to Isomers. (See Hydrocarbons of the Methane Series.)

**Law of Even Numbers of Atoms.**—The number of hydrogen atoms in the above hydrocarbons is always divisible by two. Should they therefore be partially replaced by other elements, the sum of these latter, if their valencies are expressed by odd numbers, e.g. Cl, N, and P, and of the remaining hydrogen atoms taken together must, as a necessary consequence of the law of equivalent proportions, remain an even number.

## Radicals

According to *Liebig*, radicals were groups of atoms capable of a separate existence, which played the parts of elements, and, like these latter, could combine among themselves and be exchanged from one compound to another.

Later on, the postulate that such radicals must also be capable of existing in the free state was allowed to lapse, and they were frequently defined shortly as “the residues left un-attacked by certain decompositions”.

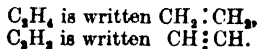
Now, however, it is usual to designate as radicals only those atomic groups which are found repeating themselves in a comparatively large number of compounds derived from one another, and which play in these compounds the part of a simple element, e.g.  $\text{CH}_3$ , methyl;  $\text{C}_2\text{H}_5$ , ethyl; by this definition the question of their existence or non-existence in the free state does not arise. Free radicals like triphenylmethyl,  $\text{C}(\text{C}_6\text{H}_5)_3$ , were detected in 1900, and free methyl and ethyl in 1929 (*Paneth*). Some of these have an extremely short life and tend to unite to form e.g. ethane,  $\text{CH}_3\cdot\text{CH}_3$ , and *n*-butane,  $\text{C}_2\text{H}_5\cdot\text{C}_2\text{H}_5$  (cf. Chap. LII, B.). In addition to univalent radicals like methyl and ethyl, bivalent, e.g.  $\text{C}_2\text{H}_4$ , ethene, and trivalent, e.g.  $\text{C}_3\text{H}_5$ , glyceryl, are also known. The monovalent residues,  $\text{C}_n\text{H}_{2n+1}$  (methyl, ethyl, &c.), which form the radicals of the monovalent alcohols,  $\text{C}_n\text{H}_{2n+1}\text{OH}$ , are frequently termed *alkyls*, or *aliphyls*, while the divalent residues,  $\text{C}_n\text{H}_{2n}$ , are known as *alkylenes*.

At the present time it is also customary to speak of single atoms as radicals; e.g. we have the chloride or iodide radical, and further, the hydrogen radical which is characteristic of acids.

### Classification of the Hydrocarbons, &c.

Most of the hydrocarbons so far mentioned are termed "saturated" compounds, since they cannot take up more hydrogen. Other hydrocarbons are poorer in hydrogen, "unsaturated", e.g.  $\text{C}_2\text{H}_4$ , ethylene, and  $\text{C}_2\text{H}_2$ , acetylene, each of which is the first member of a homologous series.

The constitution of these is explained, as will be seen later, by the assumption of a double or triple bond between neighbouring carbon atoms, for instance:



From these hydrocarbons, as starting-points, numerous substitution products, such as alcohols, aldehydes, ketones, acids, amines, &c., are derived by exchange of the hydrogen for halogen, oxygen, nitrogen, &c.

To another class of hydrocarbons belongs that most important compound, benzene,  $\text{C}_6\text{H}_6$ , which contains eight atoms of hydrogen less than hexane,  $\text{C}_6\text{H}_{14}$ , and which is regarded as a

closed chain of six carbon atoms. (See Benzene Derivatives.) From benzene are derived an immense number of homologous and analogous hydrocarbons, also substitution products, alcohols, aldehydes, acids, and so on. Thus benzene, like methane, is the mother substance of numerous organic compounds.

A closed (ring) chain is characteristic of numerous other compounds, e.g.:

(a) Trimethylene,  $C_3H_6$ ; Tetramethylene,  $C_4H_8$ ; and Penta-methylene,  $C_5H_{10}$ .

(b) Pyridine,  $C_5H_5N$ , a strongly basic nitrogenous compound, but one which at the same time resembles benzene closely in many respects.

(c) Furane,  $C_4H_4O$ ; Pyrrol,  $C_4H_5N$ ; Thiophene,  $C_4H_4S$ ; Pyrazole,  $C_3H_4N_2$ ; Thiazole,  $C_3H_3NS$ ; &c.

Some of these latter compounds closely resemble benzene, others pyridine; several of them are as yet only known in the form of derivatives. Like benzene, they are all mother-substances of—in many cases—long series of compounds.

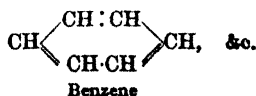
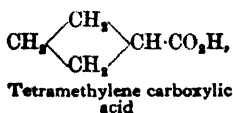
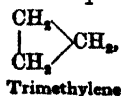
Organic chemistry is therefore divided into the following sections:

1. **Chemistry of the Methane Derivatives, Fatty Compounds, Aliphatic or Acyclic Compounds** (from *ἀλοιφή*, fat), so called because the fats and many of their derivatives belong to this group. This section comprises all carbon compounds with open chains. A few compounds, which are really closed-chain or ring compounds, will be mentioned in this section on account of their close relationship to certain open-chain compounds;

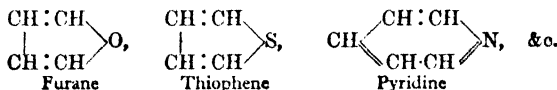
e.g. succinic anhydride  $\begin{array}{c} \text{CH}_2\text{-CO} \\ | \quad \diagup \quad \diagdown \\ \text{CH}_2\text{-CO} \end{array} \text{O}$ , which is formed by the elimination of water from succinic acid,  $\text{OH}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OH}$ .

2. **Cyclic or closed-chain compounds.** This section is usually divided into two sub-sections.

(a) Chemistry of the *carbocyclic compounds*, which comprises the study of all compounds built up of a ring of carbon atoms. As examples we have



(b) Chemistry of the *heterocyclic compounds*, comprising the study of all ring compounds which contain other atoms, in addition to carbon atoms, as part of the ring, e.g.



## Physical Properties of Organic Compounds

The physical properties of organic compounds are often of the greatest importance for their characterization, and physical data are frequently made use of in determining the purity of a chemical compound, as the pure compound has a definite melting-point or boiling-point, a definite sp. gr. and a definite solubility in a given solvent. The presence of a small amount of an impurity lowers the melting-point appreciably and also raises the boiling-point. Other physical characteristics of value are the absorption spectrum, the X-ray spectrum and the dipole moment (cf. Chap. LXXI).

**Solubility.** — The carbon compounds vary enormously as regards their solubility in various solvents. As a rule, a given solvent dissolves those substances which are chemically closely allied to it. Thus water tends to dissolve hydroxylic compounds, especially if there are several hydroxy groups in the molecule, e.g. mannitol, glucose, and pyrogallol.

Benzene tends to dissolve most hydrocarbons, and ether dissolves the majority of simple organic compounds, with the exception of salts of acids.

Details for determining solubility of solids in liquids, sp. gr., m.-pt. and b.-pt. are described in S. J., Chap II.

The methods adopted to purify organic compounds are:

1. Crystallization from a suitable solvent.
2. Distillation, fractional distillation or distillation in steam.
3. Distillation under reduced pressure.
4. Extraction of an aqueous solution with ether or other solvent not mixable with water.
5. Sublimation.

For details of these operations, cf. S. J., Chap I.

In connexion with these methods of purification several points of interest arise:

**1. Crystallization.**—It does not necessarily follow that the product is a pure compound if its melting-point is quite sharp and not affected by repeated crystallization from the same solvent. Mixed crystals of two isomorphous compounds may be present and cannot be separated by crystallization from a given solvent, but may sometimes be separated by chemical methods.

**2. Fractional Distillation.**—When the two liquids comprising the mixture form a mixture of fixed boiling-point and below that of either constituent, complete separation is impossible as this mixture distils over first when much of the higher boiling compound is present, and finally the excess of the latter. A well-known example is the aqueous solution of alcohol where, using the most effective rectifying column, the product is the constant boiling mixture containing 95.6 per cent of alcohol by weight (cf. Ethyl Alcohol, Chap. III, A.).

**3. Steam Distillation.**—The rapidity with which a given substance distils with steam depends on the vapour pressure of the substance at the given temperature, and also on its molecular weight or vapour density compared with that of water. Thus a mixture of nitro-benzene and water, which may be regarded as non-miscible liquids, boils at  $99^{\circ}$ ; i.e. the vapour pressure of the mixture at  $99^{\circ}$  is 760 mm. The vapour pressure of water at  $99^{\circ}$  is 733 mm., and therefore the partial pressure of the nitro-benzene is 27 mm. In a given volume of the mixed vapours  $\frac{733}{760}$  will consist of steam and  $\frac{27}{760}$  of nitro-benzene, and the relative weights of these volumes will be the volumes  $\times$  relative densities, i.e.  $\frac{9 \times 733}{760} : \frac{61 \times 27}{760}$ , i.e. 4 : 1; or, in other words,  $\frac{1}{5}$  by weight of the total distillate will consist of nitro-benzene.

**Extraction with Ether, Benzene, &c.—Partition Coefficient.**—An organic compound can often be separated from other substances, especially inorganic salts, by shaking out with ether, separating the ethereal layer by means of a separating funnel, drying the solution with granular calcium chloride or some other suitable drying agent, and removing the ether by distillation. The method gives very good results when the compound to be extracted is much more soluble in ether than in water, and when the substances from which it is to be

separated are insoluble in ether. When there is no marked difference in the solubilities of the given compound in ether and in water, the extraction must be repeated a number of times, in some cases even twenty, since for each compound the ratio  $\frac{\text{conc. of ethereal solution}}{\text{conc. of aqueous solution}}$  is a constant, and is usually

termed the *partition coefficient* or *coefficient of distribution* of the particular substance between the two solvents. In extractions with ether it must be borne in mind that ether dissolves to an appreciable extent in water, and also water in ether. Other liquids, such as benzene, carbon-disulphide, chloroform, &c., may be used in place of ether.

When the amount of solvent to be used is limited, it is more economical to extract two or three times with small amounts of solvent rather than only once with the whole amount. As an illustration: 11 grams of a substance and 1 litre each of the non-miscible liquids, water and benzene. The solubility of the substance in benzene is ten times its solubility in water, and it has the same molecular weight in both solvents.

*Case I.*—Extracting at once with the litre of benzene,  $\frac{\text{conc. of benzene solution}}{\text{conc. of water solution}} = \frac{10}{1}$ , i.e.  $\frac{1}{11}$  of the whole or 1 gram, remains in the water.

*Case II.*—Extract twice with 500 c.c. of benzene. After first extraction, suppose  $x$  grams passes into the benzene, then conc. of aqueous solution is  $11 - x$ , and of the benzene  $2x$ ,  $\therefore \frac{2x}{11 - x} = \frac{10}{1}$ , or  $x = 9$  (approx.), and 2 grams are left in the water.

After extraction with second quantity of benzene,  $y$  grams go into the benzene. Then  $\frac{2y}{2 - y} = \frac{10}{1}$ , or  $y = 1.7$  (approx.), and only 0.3 gram remains in the aqueous solution. Whereas, after the single extraction with a litre of benzene 1 gram was left.

For applications of this method in determining the relative strengths of acids and amines, compare *Farmer and Warth* (J. C. S., 1904, 1713).

# ALIPHATIC OR OPEN-CHAIN COMPOUNDS

## I. HYDROCARBONS

### A. Saturated Hydrocarbons, $C_nH_{2n+2}$

This constitutes the simplest homologous series of carbon compounds, and all the saturated open-chain carbon compounds may be regarded as derived from these.

The following list includes the more important *normal* hydrocarbons:\*

Formula	Name	Melting-point	Boiling-point	Specific gravity
$CH_4$	Methane	-184°	-161°	0.415 at b.-p.
$C_2H_6$	Ethane	-172°	-88°	0.446 at 0°
$C_3H_8$	Propane	-190°	-45°	0.536 at 0°
$C_4H_{10}$	Butane	-135°	+1°	0.600 at 0°
$C_5H_{12}$	Pentane	-131°	36°	0.627 at 14°
$C_6H_{14}$	Hexane	-94°	69°	0.658 at 20°
$C_7H_{16}$	Heptane	-90°	98°	0.683 at 20°
$C_8H_{18}$	Octane	-56°	125°	0.702 at 20°
$C_9H_{20}$	Nonane	-51°	150°	0.718 at 20°
$C_{10}H_{22}$	Decane	-32°	174°	0.730 at 20°
$C_{11}H_{24}$	Undecane	-26°	197°	0.774 at m.-p.
$C_{12}H_{26}$	Dodecane	-12°	216°	0.773 at m.-p.
$C_{14}H_{30}$	Tetradecane	+5°	252°	0.775 at m.-p.
$C_{16}H_{34}$	Hexadecane	20°	287°	0.775 at m.-p.
$C_{20}H_{42}$	Eicosane	37°	205°†	0.778 at m.-p.
$C_{21}H_{44}$	Heneicosane	40°	215°†	0.778 at m.-p.
$C_{23}H_{48}$	Tricosane	48°	234°†	0.779 at m.-p.
$C_{31}H_{64}$	Hentriacontane	68°	302°†	0.781 at m.-p.
$C_{35}H_{72}$	Pentatriacontane	75°	331°†	0.782 at m.-p.
$C_{40}H_{82}$	Hexacontane	101°		

\* Doss, *Physical Constants of Principal Hydrocarbons*. New York, 1939.

† Under 15 mm. pressure.

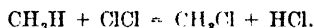


The first members of the series, including those with about four atoms of carbon, are gases, which gradually become more easily condensable as the number of carbon atoms in the molecule increases. The members which follow are liquid at the ordinary temperature, their boiling-point rising with increasing number of carbon atoms. An increase of  $\text{CH}_2$  in the molecular formula does not necessarily denote a definite increase in the boiling-point. The difference in boiling-point between ethane and propane is  $43^\circ$ , between *n*-heptane and *n*-octane  $27^\circ$ , and between undecane and dodecane only  $19^\circ$ ; thus with compounds of high molecular weight an increase of  $\text{CH}_2$  does not produce so marked an effect on the boiling-point as with simpler compounds. The higher homologues, from about  $\text{C}_{16}\text{H}_{34}$  (melting-point  $20^\circ$ ) on, are solid at the ordinary temperature, and their melting-point gradually rises up to about  $100^\circ$ . The highest members can be distilled under diminished pressure only. The methane homologues are almost or quite insoluble in water; alcohol dissolves the gaseous members to a slight extent, the liquid members easily, and the solid with gradually increasing difficulty. Their specific gravities at the melting-point increase with increasing number of carbon atoms from 0.4 up to 0.78, which is the maximum limit. This value is already almost reached by the hydrocarbon  $\text{C}_{11}\text{H}_{24}$ , so that for the higher members of the series the following law holds good: "the molecular volumes are proportional to the molecular weights" (*Krafft*).

They are incapable of combining further with hydrogen or halogens (see p. 46), and absorb neither bromine nor sulphuric acid. They are therefore termed the Saturated Hydrocarbons. Even fuming nitric acid has little or no action upon the lower members of the series; thus, methane is not attacked by a mixture of fuming nitric and sulphuric acids, even at  $150^\circ$ . The *n*-compounds are only slightly acted upon by nitric acid at  $100^\circ$  (*Francis and Young*, J. C. S., 1898, 923; *Markownikoff*, B., 1899, 1441), whereas tertiary hydrocarbons  $\text{CHR}'\text{R}''\text{R}'''$  are fairly readily oxidized by fuming nitric acid to fatty acid,  $\text{CO}_2$  and nitro compounds. Nitro groups can be introduced into paraffins by heating them with dilute nitric acid (D. 1.07–1.15) at  $110$ – $120^\circ$  under pressure, or with  $\text{N}_2\text{O}_4$  (C. R., 1937, 204, 870) at  $20^\circ$ . They are indifferent to sulphuric acid (cf. Olefines and Benzenes), even fuming (15 per cent) acid in the cold; prolonged action of hot concentrated

acid yields sulphonic acids with those members with branched chains. They are also very indifferent towards chromic acid and permanganate of potash in the cold, with the exception of the tertiary hydrocarbons; when oxidation does take place, they are mostly converted directly into carbonic acid. The name of "The Paraffins" (from *parum affinis*), which was originally applied only to the solid hydrocarbons from lignite, has therefore been extended to the whole homologous series.

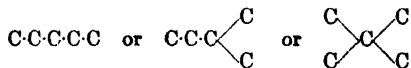
By the action of the halogens (Cl, Br), **substitution** takes place, the substituted hydrogen combining with an amount of halogen equal to that which has entered the hydrocarbon (see Halide Substitution Products of the Hydrocarbons, p. 60):



As the number of carbon atoms increases, the percentage composition of these hydrocarbons approaches a definite limit, viz. that of the hydrocarbons,  $\text{C}_n\text{H}_{2n}$ , or  $\text{CH}_2$ .

Thus the percentages of C and H in the following hydrocarbons are:  $\text{CH}_4$  75 and 25;  $\text{C}_6\text{H}_{14}$  83.72 and 16.28;  $\text{C}_{22}\text{H}_{46}$  85.16 and 14.84;  $\text{C}_{35}\text{H}_{72}$  85.36 and 14.64, whereas for  $\text{CH}_2$  the values are 85.71 and 14.29. It is therefore impossible to deduce a definite formula for complex hydrocarbons by analysis only; the only reliable data here are the methods of formation from compounds in which the number of carbon atoms in the molecule is already known.

*Isomers.*—The first 3 members exist in one form only, but two butanes, three pentanes and five hexanes are known, and most of the higher hydrocarbons are known in various isomeric forms. To account for these phenomena it is concluded that the carbon atoms are grouped in different ways in the isomerides, e.g. in straight chains and in various branching chains. (This is of course not to be taken as meaning that they are grouped together in space in straight lines.) Thus:



Those with non-branching chains are termed the normal hydrocarbons; the second, the iso-hydrocarbons.

The principles by which such constitutional formulæ are arrived at will be explained under Butane and Pentane.

Only those homologues are comparable whose constitutions are similar, e.g. the normal hydrocarbons.

*Occurrence.*—Many hydrocarbons of the paraffin series occur naturally in large quantities. Thus, methane is exhaled from the earth's crust, as "fire-damp" and as marsh-gas. The next higher homologues are found dissolved in petroleum, which also contains the higher hydrocarbons in large amount. Solid hydrocarbons occur as ozokerite or earth-wax. By the fractional distillation of petroleum a large number of these compounds have been isolated. Heptane and hexadecane are also found in the vegetable kingdom.

*Modes of formation.*—A. Various members of this series are obtained by the distillation of lignite (Boghead, Cannel coal), wood, bituminous shale, and, in very much smaller quantity, from pit coal. Paraffins are also obtained by dissolving carbide of iron in acids, and by heating wood, lignite, and coal, but not graphite, with hydriodic acid.

B. From substances containing an equal number of carbon atoms in the molecule.

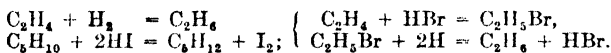
1. From the alkyl halides,\*  $C_nH_{2n+1}X$ , and, generally speaking, from the substitution products of the hydrocarbons by exchange of the halogen for hydrogen (*inverse substitution*). This is effected by the action of reducing agents, that is, agents which give rise to nascent hydrogen. Some of the commoner reducing agents employed for such purposes are sodium amalgam and water, zinc and a dilute acid, zinc and water at  $160^\circ$ , the copper-zinc couple in presence of water and alcohol (*Gladstone-Tribe*), aluminium- or magnesium-amalgam and alcohol, and one of the most vigorous reducing agents, concentrated hydriodic acid at high temperatures, especially in contact with red phosphorus, which serves continually to renew the hydrogen iodide. (See Chap. XLVII, Reduction.)

2. From monohydric alcohols,  $C_nH_{2n+1}\cdot OH$ , polyhydric alcohols,  $C_nH_{2n}(OH)_2$ ,  $C_nH_{2n-1}(OH)_3$ , &c., also from aldehydes,  $C_nH_{2n+1}\cdot CHO$ , ketones,  $C_nH_{2n+1}\cdot CO\cdot C_nH_{2n+1}$ , and other compounds containing oxygen, by heating with hydriodic acid and red phosphorus at relatively high temperatures. In all these reactions the oxygen is ultimately removed as water.

3. From hydrocarbons poorer in hydrogen, i.e. unsaturated hydrocarbons (see these), by the addition of hydrogen; e.g. ethane from ethylene or acetylene and hydrogen, either in

\* The monovalent residues,  $C_nH_{2n+1}$ , methyl, ethyl, &c., which are at the same time the radicals of the monohydric alcohols,  $C_nH_{2n+1}OH$ , are frequently termed alkyl groups.

presence of platinum black or finely divided nickel or by heating the mixture of gases to  $400^{\circ}$ – $500^{\circ}$ . Also by heating with hydriodic acid (*Krafft*), or by addition of halogen or halogen hydride, and exchange of the halogen for hydrogen, according to 1. Thus:

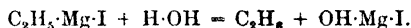


Some of the cyclo-paraffins (Chap. XVI) with hydrogen and a metallic catalyst yield open-chain paraffins: cyclo-propane and  $\text{H}_2 \rightarrow$  propane.

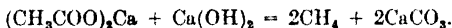
4. By decomposing the organo-zinc compounds (zinc-alkyls) with water (*Frankland*):



Or more readily by decomposing *Grignard's* organo-magnesium compounds with water. Thus ethyl iodide and magnesium, in presence of dry ether, yield ethyl magnesium iodide,  $\text{C}_2\text{H}_5\cdot\text{Mg}\cdot\text{I}$ , and this with water evolves ethane:



C. From acids containing a larger number of carbon atoms, with separation of carbon dioxide. Thus, by heating acetate of calcium with soda-lime, methane and calcium carbonate are formed:



In the case of the acids of higher molecular weight, this separation of carbonic acid is conveniently effected by heating with sodium ethoxide.

D. By the combination of two radicals containing a smaller number of carbon atoms.

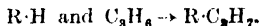
1. By the action of sodium upon the alkyl iodides in ethereal solution (*Wurtz*); or with magnesium or by heating with zinc in a sealed tube (*Frankland*):



By this method also two different radicals can be combined, e.g.  $\text{C}_2\text{H}_5\text{I} + \text{C}_4\text{H}_9\text{I}$  give  $\text{C}_2\text{H}_5 + \text{C}_4\text{H}_9 = \text{C}_6\text{H}_{14}$ , ethyl-butyl (*Wurtz's* "Mixed Radicals").

*Grignard's* compounds (Chap. IV, H.) can also be used  $\text{R}\cdot\text{MgI} + \text{R}'\text{I} \rightarrow \text{R}\cdot\text{R}' + \text{MgI}_2$ , and in some cases, in place of an alkyl iodide a di-alkyl sulphate or an alkyl *p*-toluene-sulphonate can be used.

2. A paraffin will combine with an olefine ( $C_3$  to  $C_5$ ) in the presence of  $AlCl_3$  giving a higher paraffin (*Ipatieff*, J. A. C. S., 1936, 913).



3. By the electrolysis of solutions of the potassium salts of fatty acids (*Kolbe*, 1848). The anions, for example,  $CH_3 \cdot COO$ , when discharged at the anode, break up into  $CH_3$  and  $CO_2$ , and two of the  $CH_3$  groups immediately combine to form a molecule,  $CH_3 \cdot CH_3$ , viz. ethane. The hydrogen is here evolved at the cathode, and the hydrocarbon at the anode; the carbon dioxide is to a large extent retained in the solution.

**Methane,  $CH_4$**  (*Volta*, 1778). *Occurrence*.—As an exhalation from the earth's crust, more especially at Baku in the neighbourhood of the Caspian Sea (the "Holy Fire" of Baku); from the large gas wells at Pittsburg, in North America, and in numerous other places; in the exhalations from mud volcanoes, for instance at Bulganak in the Crimea, where the gas is almost pure methane (*Bunsen*); and as pit gas or "fire-damp" in mines, where, when mixed with air, it is apt to cause explosions.

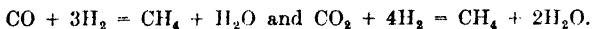
As marsh-gas, together with carbon dioxide and nitrogen, by the decomposition of organic substances under water; further, by the fermentation of cellulose, e.g. by river mud, by means of *Schizomycetes* (fission-fungi). It is also found in rock-salt (the Knistersalz of Wieliczka), and in the human intestinal gases (up to 57 per cent  $CH_4$  after eating pulse).

The illuminating gas obtained by the destructive distillation of coal contains about 40 per cent methane.

*Modes of preparation*.—1. Methane is formed synthetically by the direct union of carbon and hydrogen. Pure sugar carbon freed from all traces of hydrogen by treatment with chlorine is heated in a current of dry hydrogen in a porcelain tube, and the issuing gas is found to contain 1 per cent of methane (*Bone and Jerdan*, J. C. S., 1897, 41; 1901, 1042; *Pring*, 1910, 489; *Pring and Fairlie*, 1911, 1796; 1912, 91). At  $475^\circ$ , in contact with an active form of carbon (gas-black) and finely divided nickel, a product containing 50 per cent of methane is obtained. It is also formed by the decomposition of ethane, ethylene, and acetylene at moderate temperatures (*Bone and Coward*, 1908, 1197; *Travers and Pearce*, J. S. C. I., 1934, 321 T).

2. By the catalytic reduction of carbon monoxide or dioxide

by hydrogen in the presence of reduced nickel at 200–250 (*Sabatier* and *Senderens*), a method used for removal of CO from water gas whereby the calorific value is increased:



3. By leading sulphuretted hydrogen and carbon bisulphide vapour over red-hot copper (*Berthelot*);  $\text{CS}_2 + 2\text{H}_2\text{S} + 8\text{Cu} = \text{CH}_4 + 4\text{Cu}_2\text{S}$ .

4. By passing carbon monoxide and steam over certain heated metals or metallic oxides (*Vignon*, C. R., 1913, **157**, 131).

5. It is usually prepared by heating anhydrous sodium acetate with baryta, or even with soda-lime (p. 33); by-products are ethylene,  $\text{C}_2\text{H}_4$ , and hydrogen (up to 8 per cent).

6. Another method is from aluminium carbide and water, and removing the acetylene and hydrogen (J. C. S., 1913, 1292).

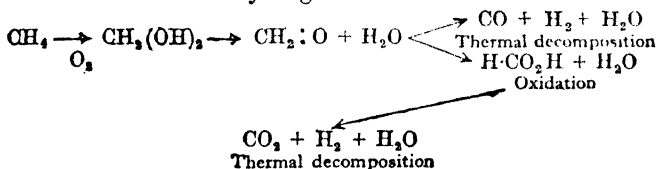
7. Pure methane is obtained from magnesium methyl iodide and water,  $\text{CH}_3\text{MgI} + \text{H}\cdot\text{OH} = \text{CH}_4 + \text{OH}\cdot\text{MgI}$ ; by the reduction of methyl iodide,  $\text{CH}_3\text{I}$ , e.g. in alcoholic solution by means of zinc in the presence of precipitated copper (the *Gladstone-Tribe* "Copper-zinc Couple"); also by the inverse substitution of  $\text{CHCl}_3$ , or  $\text{CCl}_4$ .

*Properties* (for summary, see J. ph. Chem., 1918, 529).—It is a gas with a density 8( $\text{H} = 1$ ), and is condensed under a pressure of 140 atmospheres at  $0^\circ$ . It boils at  $-161^\circ$ , and solidifies at  $-184^\circ$ . Absorption coefficient in cold water about 0.5. It burns with a pale and only faintly luminous flame, yielding carbon dioxide and water, and when mixed with air or oxygen in certain proportions forms an explosive mixture. It is decomposed by the electric spark into its elements, and a similar decomposition occurs when the gas is led through a red-hot tube; but there are formed at the same time  $\text{C}_2\text{H}_6$ ,  $\text{C}_2\text{H}_4$ ,  $\text{C}_2\text{H}_2$ , and, in smaller quantity,  $\text{C}_6\text{H}_6$ , benzene,  $\text{C}_{10}\text{H}_8$ , naphthalene, and other products. The first three hydrocarbons just mentioned, ethane, &c., behave similarly.

**Combustion of Hydrocarbons.**—When methane and hydrocarbons generally are burnt or exploded with excess of air or oxygen, the final products are carbon dioxide and water vapour, and the reaction is generally represented, e.g. by the equation  $\text{CH}_4 + 2\text{O}_2 = \text{CO}_2 + 2\text{H}_2\text{O}$ . This undoubtedly represents the final products which are formed, and also their relative amounts, but does not give an idea of the mechanism of com-

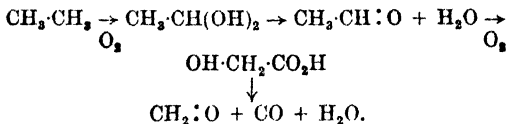
bustion. Numerous investigators have conducted experiments on combustion, especially on combustion in the presence of limited amounts of oxygen. The conclusion was first drawn that with a defective supply of oxygen the hydrogen is oxidized in preference to the carbon. Somewhat later, *Kersten* (1861) suggested the preferential burning of the carbon, since when ethylene is exploded with its own volume of oxygen, carbon monoxide and hydrogen are the chief products. (Cf. *Smithells*, J. C. S., 1892, 220.)

The work of *Bone* and others on the slow combustion of methane, ethane, ethylene, and acetylene (J. C. S., 1902, 535; 1903, 1074; 1904, 693, 1637; Proc. 1905, 220; B. A. Report, 1910, 469; J. S. C. I., 1933, 202 T; C. and I., 1933, 905; 1936, 174), show that by passing a mixture of methane and oxygen in a continuous stream through a tube filled with porous material (pot or magnesia), at a fixed temperature between 350° and 500°, appreciable amounts of formaldehyde are obtained. Gaseous products are also obtained, but these are probably due to secondary reactions, e.g. either the further oxidation of the aldehyde to carbon monoxide, carbon dioxide and steam, or the thermal decomposition of the aldehyde into carbon monoxide and hydrogen. Thus:



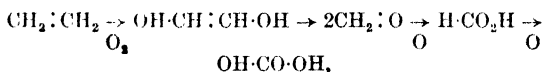
By the expression thermal decomposition is meant that at the temperature mentioned the aldehyde is unstable, and immediately decomposes into the simpler products, CO and H<sub>2</sub>.

Ethane behaves similarly, and the reactions can be represented by the following scheme:



Secondary reactions are the thermal decompositions of the formaldehyde into CO and H<sub>2</sub>, and of the acetaldehyde into CH<sub>4</sub> and CO. In reality some 80 per cent of the ethane can

be collected as formaldehyde. With ethylene the reactions are probably:



and the thermal decomposition products of the formaldehyde, formic acid, and carbonic acid, viz.  $\text{H}_2$ ,  $\text{CO}$ ,  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ .

It is thus obvious that at the temperatures mentioned (350–500°) combustion consists primarily in the addition of oxygen and the production of hydroxylic compounds, which then yield aldehydes. It is highly probable that reactions of a similar nature occur during explosive combination and detonation at high temperatures (B. A. Report, 1910, 492).

**Ethane**,  $\text{C}_2\text{H}_6$ , occurs in crude petroleum and is a constituent of the gas obtained from American oil wells and can be utilized for technical purposes.

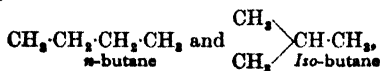
*Preparation.*—By the electrolysis of acetic acid (*Kolbe*, 1848), and therefore formerly called “methyl” since it was supposed to be  $\text{CH}_3$ ; subsequent molecular-weight determinations proved it to have the double formula  $\text{C}_2\text{H}_6$ . It is also obtained from ethyl iodide, alcohol, and zinc dust, or from zinc ethyl (*Frankland*), hence the name “ethyl hydride”. “Ethyl hydride” and “methyl”, which were formerly supposed by *Frankland* and *Kolbe* to be different substances, were proved identical by *Schorlemmer* in 1863 by their conversion into  $\text{C}_2\text{H}_5\text{Cl}$ , which may be prepared from both in exactly the same way.

**Propane**,  $\text{C}_3\text{H}_8$ , and the two butanes,  $\text{C}_4\text{H}_{10}$ , are also gaseous at the ordinary temperature, and are present to a certain extent in crude petroleum.

Theoretically propane can exist in only one form, represented by the constitutional formula  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_3$ , as this is the only manner in which three carbon and eight hydrogen atoms can be grouped if C is quadri- and H univalent.

## ISOMERISM, NOMENCLATURE, CONSTITUTION

From propane,  $\overset{\alpha}{\text{CH}}_3\cdot\overset{\beta}{\text{CH}}_2\cdot\overset{\alpha}{\text{CH}}_3$ , it is clear that the two distinct products



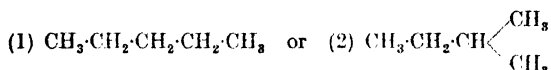


can be obtained theoretically by replacing either one of the  $\alpha$ H or one of the  $\beta$ H atoms by methyl.

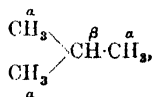
Two compounds  $C_4H_{10}$  are actually known, and their constitutional formulæ derived from their methods of formation agree with the two formulæ  $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_3$  and  $(CH_3)_2 : CH \cdot CH_3$ , as the *n*-compound may be obtained by the action of zinc on ethyl iodide,  $CH_3 \cdot CH_2I$ , and the *iso*-compound by the reduction of tertiary butyl iodide,  $(CH_3)_2 : CI \cdot CH_3$ .

All the succeeding hydrocarbons can, according to theory, exist in several isomeric modifications. The number of modifications possible can be determined in the manner already described for the butanes.

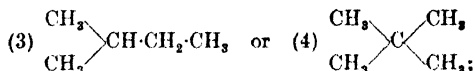
As an example, starting with *n*-butane,  $\overset{\alpha}{CH_3} \cdot \overset{\beta}{CH_2} \cdot \overset{\beta}{CH_2} \cdot \overset{\alpha}{CH_3}$ , and replacing one H atom by a  $CH_3$  group, we can get either



according as we replace an H atom in the  $\alpha$  or  $\beta$  position. Starting from *iso*-butane,



we can similarly get



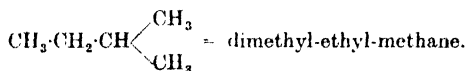
but formulæ (2) and (3) are identical, and the three possible isomeric pentanes are therefore  $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_3$ ,  $(CH_3)_2 : CH \cdot CH_2 \cdot CH_3$  and  $(CH_3)_2 : C : (CH_3)_2$ . Of hydrocarbons with six carbon atoms, five isomers are possible, and they are all known. Of the nine possible heptanes,  $C_7H_{16}$ , the existence of five has already been proved.

The number of theoretically possible isomers increases very rapidly with the number of carbon atoms, so that 159 isomeric  $C_{10}$  hydrocarbons are possible although only 2 are known and  $C_{20}$  gives 115,000 possible isomerides.

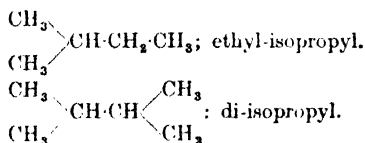
Of these isomers only one can be **normal**, i.e. can have a single chain of carbon atoms, in which each of the two terminal

carbon atoms is combined with three atoms of hydrogen, and all the middle ones with two, according to the formula,  $\text{CH}_3 \cdot (\text{CH}_2)_n \cdot \text{CH}_3$ .

A convenient *Nomenclature* for the more complicated paraffins is arrived at by making methane the starting-point for all of them, that carbon atom from which the branching chain emanates being considered as originally belonging to  $\text{CH}_4$ , in which the hydrogen atoms are supposed to be wholly or partially replaced by hydrocarbon radicals, thus:



The names of the well-known lower hydrocarbon radicals (alkyls) are also frequently used as a basis; for instance, the group  $(\text{CH}_3)_2\text{CH}$  is termed isopropyl (see Isopropyl Alcohol), hence the compounds:



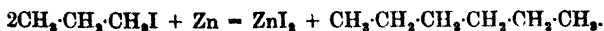
The boiling-points of the normal hydrocarbons are always higher than those of the isomers; indeed the boiling-point falls continuously as the carbon chain becomes more branched.

The *Constitution* of the higher paraffins can in most cases only be arrived at with certainty from their synthetical formation (e.g. normal butane and hexane), or from their chemical relation to oxygenated derivatives whose constitution is already known, especially to the ketones and acids. (See Ketones.)

If, for instance, by the action of  $\text{PCl}_5$  upon acetone, for which the constitution  $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_3$  is proved, the substance  $\text{CH}_3 \cdot \text{CCl}_2 \cdot \text{CH}_3$  (acetone chloride) be formed, and this be then treated with zinc methyl, the resulting hydrocarbon, a pentane, will have the constitution  $(\text{CH}_3)_4\text{C}$ :



The structure of *n*-hexane follows from its formation by the action of metals upon *n*-propyl iodide, as represented by the equation:



The system of nomenclature suggested by the International Congress at Geneva is as follows: The normal paraffins retain their present names. Thus hexane means the compound  $\text{CH}_3 \cdot (\text{CH}_2)_4 \cdot \text{CH}_3$ . In the case of those with branching chains, the longest normal chain gives the name, the branches being regarded as substituents, and the position of substitution being indicated by the successive numbering of the atoms of the carbon chain (the carbon atom which is nearest to the point of ramification is numbered 1; should there be more than one branching—say, a longer and a shorter—then No. 1 begins with the end carbon atom which stands nearest to the shorter branching). Trimethyl-methane is therefore called 2-methyl-propane; dimethyl-ethyl-methane, 2-methyl-butane; and tetra-methyl-methane, 2 : 2-dimethyl-propane.

The following liquid paraffins are obtained from crude petroleum: *n*-compounds with 5 to 10 C atoms and an isomeride of each,\* and a large number of the higher hydrocarbons.

*F. Krafft* has prepared the normal hydrocarbons from  $\text{C}_{11}\text{H}_{24}$  to  $\text{C}_{35}\text{H}_{72}$ , which are mentioned in the table on p. 29, from the acids  $\text{C}_{12}$ ,  $\text{C}_{14}$ ,  $\text{C}_{16}$ , and  $\text{C}_{18}$  of the acetic acid series (see these), for which the normal constitution, i.e. non-branching carbon chain, has been demonstrated; and also from the ketones,  $\text{C}_n\text{H}_{2n}\text{O}$ , which are obtained by subjecting the barium salts of these acids to dry distillation, either alone or together with acetate or heptoate of calcium, and which, as a consequence of their mode of formation, yield normal hydrocarbons. (See Ketones.) *Krafft* has further isolated the normal hydrocarbons  $\text{C}_{17}\text{H}_{36}$  to  $\text{C}_{23}\text{H}_{48}$ , also  $\text{C}_{24}\text{H}_{50}$ ,  $\text{C}_{26}\text{H}_{54}$ , and  $\text{C}_{28}\text{H}_{58}$ , by subjecting the paraffin obtained from lignite to fractional distillation *in vacuo*.

These are, from about  $\text{C}_{16}\text{H}_{34}$  (m.-pt.  $18^\circ$ ) on, solid at the ordinary temperature. When distilled under atmospheric pressure the higher hydrocarbons partially decompose into lower ones of the formulæ  $\text{C}_n\text{H}_{2n+2}$  and  $\text{C}_n\text{H}_{2n}$ ; but they may be distilled under reduced pressure. (See table, p. 29.)

**Mineral Oils.**—**Petroleum** and similar products obtained by heating bituminous shale are usually termed mineral oils, in order to differentiate them from vegetable and animal oils, from which they differ in composition.

\* The petroleum ether and ligroin of commerce consist principally of the hydrocarbons  $\text{C}_6\text{H}_{14}$ ,  $\text{C}_7\text{H}_{16}$ , and  $\text{C}_8\text{H}_{18}$ .

In many parts of the earth's surface oil rises in the form of springs when bore-holes are made into sand or conglomerate, and the product is the crude petroleum of commerce. Such wells or springs were first discovered in 1859 in Pennsylvania, and since then similar sources have been utilized in the Caspian Sea district (Baku), in Galicia, Roumania, Burma, Assam, Borneo, Mexico, South Persia, Trinidad and Japan, and in smaller quantities in other parts. In America the oil is accompanied by natural gas consisting largely of the lower paraffin hydrocarbons, and can be used as gaseous fuel (cf. C. I., 1937, 520). The crude petroleum cannot be used as such, and has to be subjected to a process of fractional distillation and refining by means of sulphuric acid and caustic soda, or by a process of compression and fractionization into a low boiling petrol with strong anti-knock properties. The natural gas is also subjected to a process of pyrolysis yielding olefines which polymerize, yielding valuable motor spirit. Certain hydrocarbons are also isolated and converted into various derivatives of technical value. As a rule, the crude oil is carried long distances to the refining factory, usually in iron pipes 4-8 inches diameter. The pipe line is frequently several hundred miles long, in stages of 50 miles, with tanks at intervals. The object of the refining is to obtain products of commercial importance and to remove impurities which would affect the values of the fractions, such as tarry or resinous substances and sulphur.

In the American industry a great variety of products is thus obtained, to which different names are given.

			B.P.	Amount
Cymogene	..	..	0°	16.5 per cent.
Rhigoline	..	..	18°	
Gasoline	..	..	14-90°	
Ligroin	..	..	90-120°	
Benzene or Benzoline	..	..	120-150°	54.0 "
Kerosene	..	..	150-300°	
Lubricating oil	..	..	..	
Vaseline	..	..	..	
Paraffin wax, m.p.	..	..	45-65°	2.0 "

Liquefied cymogene is used for ice manufacture. Rhigoline is used in medicine as a local anæsthetic. The next three fractions are used for extracting oils and fats and for dry cleaning. The petrol used in internal-combustion engines usually boils at 70-140°, but at the present time contains less

low-boiling constituents than formerly. The kerosene required for illuminating purposes should be water-white, and should not have too low a "flash point". Crude kerosenes and lubricating oils are used for making "oil-gas", small installations of which are used in place of coal-gas plants. The higher fractions are used as lubricants, and have the advantage over vegetable-oil lubricants; they are chemically inactive, whereas vegetable oils can undergo hydrolysis, and give rise to fatty acids which may have a corroding action on the machinery. These higher oils are also used as fuels; when blown through a nozzle, or "atomizer", in the form of a fine spray they can be burnt under boilers for generating steam, or they may be used in Diesel engines.

When the oil-wells were first started the chief commercial product was the kerosene, or burning oil, and the lower fractions were largely waste products; the introduction of the internal-combustion engine in automobiles and aeroplanes has created an enormous demand for petrol, and at the present time the supply cannot meet this demand, and other materials have been introduced, the most important of which are benzene and methyl and ethyl alcohols. The demand for petrol has also led to the introduction of methods of breaking up the heavier oils by the process of cracking, i.e. subjecting the oils to high temperatures, usually under increased pressure. The products vary with the temperature, rate of flow of the oil, construction of the retort, e.g. presence of baffle plates, and the pressure in the retort. Better yields are obtained by using a catalyst, e.g. hydrated aluminium silicate, and lower temperatures and pressures. The cracked spirit is richer in unsaturated naphthene and aromatic hydrocarbons than a straight run spirit, and most motor fuels are blends of the two. The "antiknock" properties of a fuel are improved by the presence of a branched paraffin, e.g. *iso*-octane,  $\text{CMe}_3\cdot\text{CH}_2\cdot\text{CHMe}_2$ , and large quantities of this are manufactured from *iso*-butane and 1-butene in the presence of sulphuric acid or aluminium chloride (p. 34, also C. I., 1936, 532; 1941, 22). The olefines formed during cracking are often absorbed by concentrated sulphuric acid and used for preparing alcohols, e.g. ethyl, *iso* propyl, secondary -butyl and -amyl alcohols (p. 77).

*Composition of Natural Petroleum.*—The American oil consists mainly of paraffin hydrocarbons, e.g. gasolene is largely pentane

and hexane, and kerosene contains hydrocarbons from  $C_{10}H_{22}$  to  $C_{16}H_{34}$ . Russian Petroleum, on the other hand, contains appreciable amounts of polymethylene hydrocarbons or naphthenes (Chap. XVI) and of acids derived from them, and gives small yields of low-boiling fractions. Borneo oil contains appreciable amounts of aromatic hydrocarbons, e.g. benzene and toluene, &c., and Burma oil is rich in wax.

*Origin of Petroleum.*—One view is that the oil is formed by the action of steam on carbides of iron and other metals under considerable pressure in the lower portion of the crust of the earth (*Mendeleff*). Another view is that the oil is a product of decomposition of animal or vegetable organisms (*Engler*, C. Z., 1906, II, 1017; compare *Kishner*, J. russ., 1914, **46**, 1428), and this view is supported by the fact that many paraffin oils have a low-optical activity, due probably to the presence of optically active polynaphthenes and organic compounds containing N and S (*C. Zeit.*, 1913, **37**, 550).

The total output of crude petroleum for 1937 was estimated at about 280 million tons, of which 62 per cent came from the U.S.A., 10.1 per cent from Russia, 9.9 per cent from Venezuela, and 5 per cent from Iran and Iraq.

## Production of Organic Chemicals from Petroleum \*

From natural gas and gasoline appreciable quantities of *n*- and *iso*-pentane are now isolated in America and are utilized for making mono-, di-chloro derivatives, the monohydric alcohols (viz. *n*-butyl-carbinol, *iso*-butyl-carbinol, methyl-propyl-carbinol, di-ethyl-carbinol), amylenes, amyl sulphide, amyl-mercaptan and amyl-amines.

The gases obtained by cracking petroleum either in the gaseous or liquid phase contain appreciable amounts of olefines and also of dienes. With liquid phase at 450–480° the olefine content of the gas is low (8–13 per cent), and rather poor in ethylene; with gaseous phase at 600° the olefine content is high (30–75 per cent), and the proportion of ethylene in the olefines may be as high as 25 per cent.

The compounds actually manufactured are: ethylene, as

\* Carelton Ellis, *Chemistry of Petroleum Derivatives*, 1934.

an anæsthetic or for ripening fruit; ethylene dichloride and ethylene glycol, the former for use as a solvent or for fumigating grain, and the latter as a substitute for glycerol; ethylene di-amine as an accelerator in vulcanization; ethylene chlor-hydrin for manufacture of novocaine, procaine and indigo; ethylene oxide, which with alcohol, gives the glycol monoethyl ether used as a solvent for cellulose esters.

One of the chief uses of the cracked gases is for the production of alcohols by absorbing the different olefines in concentrated sulphuric acid of different concentrations (cf. p. 77).

**Shale Oil.**—Large quantities of shale oil are distilled in continuous retorts in Scotland, and products analogous to those derived from crude petroleum, including ammonia, phenols and paraffin wax, are obtained, and from low-grade cannel coals or brown coals at suitable temperatures similar products are formed. Such oils differ entirely from the oils obtained from coal in the process of manufacturing coke or coal-gas. (Cf. Chap. XVII, Coal Tar.)

In the manufacture of shale and brown coal oils, appreciable amounts of ammonia are produced. A shale containing 63–80 per cent of mineral matter yields about 20 gall. of crude oil and 44 lb. of ammonium sulphate per ton of shale.

**Paraffin-Wax**, obtained by *Reichenbach* in 1830 from wood-tar, is got by the distillation of lignite or peat. It is also a mixture of many hydrocarbons, about 40 per cent of it consisting of the compounds  $C_{22}H_{46}$ ,  $C_{24}H_{50}$ ,  $C_{26}H_{54}$ , and  $C_{28}H_{58}$ .

**Liquid Paraffin** (*Reichenbach's* "Eupion") and the butter-like **Vaseline** are high-boiling distillation products of lignite or petroleum, and the same applies to many lubricating oils. Vaseline is also obtained by decolorizing the residues obtained in distilling crude petroleum.

**Ozokerite**, green, brown, and red, and of the consistency of wax, melting-point  $60\text{--}80^\circ$ , is a natural paraffin found at Boryslaw in Galicia, and at Tscheleken near Baku, on the Caspian Sea, and forms the ceresine of commerce when bleached.

**Asphalt**, or **Earth Pitch**, found in India, Trinidad, Java, and Cuba, is a transformation product of the higher-boiling mineral-oils, produced by the action of the oxygen of the air just as paraffin absorbs oxygen and becomes brown upon prolonged heating in the air. It is used for cements and salves, and in asphaltting, photo-lithography, &c.

## B. Olefines or Hydrocarbons of the Ethylene Series (Alkylenes): $C_nH_{2n}$

There are two series of hydrocarbons of the general formula  $C_nH_{2n}$ , the members of which differ from the corresponding paraffins by containing two atoms of hydrogen less in the molecule. The one series is that of the **Olefines**, of which ethylene,  $C_2H_4$ , is the first member; the other is that which contains **Trimethylene**, **Tetramethylene**, **Hexamethylene**, &c. (Cf. Chap. XVI, Polymethylenes.)

The properties exhibited by these two series are so different that different constitutions must be accorded to them. The olefines form additive compounds with exceptional facility, being thus converted into the paraffins or their derivatives;

### OLEFINES

		Melting-point	Boiling-point
Ethylene .. ..	$C_2H_4$	$-169^\circ$	$-104^\circ$
Propylene .. ..	$C_3H_6$	$-185^\circ$	$-48^\circ$
		$-130^\circ$	$-5^\circ$
Butylene (3) .. ..	$C_4H_8 \begin{cases} \alpha \\ \beta \\ \gamma \end{cases}$		$+1^\circ$
			$-6^\circ$
Amylene (5) .. ..	$C_6H_{10}^*$	$-98^\circ$	$+39^\circ$
Hexylene .. ..	$C_6H_{12}$		$68^\circ$
Heptylene .. ..	$C_7H_{14}$		$95^\circ$
Octylene .. ..	$C_8H_{16}$		$123^\circ$
Nonylene .. ..	$C_9H_{18}$		$153^\circ$
Decylene .. ..	$C_{10}H_{20}$		$172^\circ$
Undecylene .. ..	$C_{11}H_{22}$		$195^\circ$
Dodecylene .. ..	$C_{12}H_{24}$	$-31^\circ$	$\{96^\circ \dagger$
Tridecylene .. ..	$C_{13}H_{26}$		$233^\circ$
Tetradecylene .. ..	$C_{14}H_{28}$	$-12^\circ$	$\{127^\circ$
Pentadecylene .. ..	$C_{15}H_{30}$		$247^\circ$
Hexadecylene (Cetene) ..	$C_{16}H_{32}$	$+4^\circ$	$\{274^\circ$
			$\{155^\circ$
			$\{179^\circ$
Octadecylene .. ..	$C_{18}H_{36}$	$18^\circ$	
Eicosylene .. ..	$C_{20}H_{40}$		
Ceretone .. ..	$C_{27}H_{54}$	$58^\circ$	
Melene .. ..	$C_{30}H_{60}$	$62^\circ$	

\* The melting- and boiling-points given from  $C_6H_{10}$  on, are those of the normal hydrocarbons.

† { signifies boiling-point under 15 mm. pressure.



from this the conclusion is drawn that, like the latter, they contain an open carbon chain.

The names given to the hydrocarbons are similar to those for the paraffins, *except* that the termination *ane* is replaced by *ene*, or often by *ylene*.

The general formula  $C_nH_{2n}$  for this series indicates that each member differs from the corresponding member of the paraffins by two hydrogen atoms.

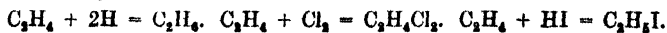
In their physical properties they resemble the methane homologues very closely.  $C_2H_4$ ,  $C_3H_6$ , and  $C_4H_8$  are gases,  $C_5H_{10}$  a volatile liquid, the higher members liquids with rising boiling-point and diminishing mobility, while the highest are solid and similar to paraffins. The boiling-points of members of both series containing the same number of carbon atoms, and whose constitutions are comparable, lie very close together, but the melting-points of the olefines are somewhat the lower of the two; e.g.  $C_{16}H_{32}$ , m.-pt.  $21^\circ$ , b.-pt.  $\{157^\circ$ , and  $C_{16}H_{32}$ , m.-pt.  $4^\circ$ , b.-pt.  $\{155^\circ$ .

Most of the olefines are readily soluble in alcohol and ether, but insoluble in water, only the lower members dissolving slightly in the latter. The specific gravities of the normal olefines, determined at the melting-points, rise from about 0.63 upwards, and approach with increasing carbon to a definite limit, viz. about 0.79.

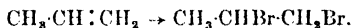
The heat of combustion of an olefine is less than that of its analogous paraffin, and hence the heat of formation is greater, viz. some 44 Cal. (cf. Heats of Formation, Chap. LXXI, C.).

The chemical properties of the olefines are quite different from those of the paraffins. The latter are comparatively inert; they are not readily oxidized, and do not form additive compounds, but can yield substitution products with halogens. The olefines, on the other hand, are chemically reactive. They are *unsaturated*, i.e. they can form additive compounds with elements or compounds without a fission of their molecules (cf. Chap. LI, A., Unsaturation), and are readily oxidized. These characteristic chemical properties are usually attributed to the presence of a double bond or linking between two carbon atoms, and this is usually termed an olefine linking, e.g.  $CH_2:CH_2$ .

(a) *Additive reactions*.—They all combine with  $H_2$ ,  $Cl_2$ ,  $Br_2$ ,  $(CNS)_2$ ,  $HI$ ,  $HClO$ ,  $HBrO$ ,  $N_2O_4$ ,  $H_2SO_4$  (fuming), yielding paraffin hydrocarbons or their derivatives:

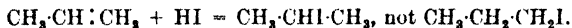


In all these reactions the double-linking characteristic of the olefines becomes replaced by a single bond, and two monovalent groups or atoms become attached to the carbon atoms which were previously united by the double bond. It follows that a dibromide formed from an olefine and bromine will always have the two bromine atoms attached to adjacent carbon atoms. (Cf. Chap. XVI, Polymethylene Derivatives.)

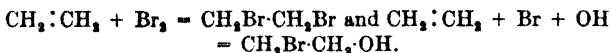


Addition of hydrogen can be effected in a variety of different ways, e.g. (a) by the use of reducing agents, i.e. the addition of nascent hydrogen; sodium amalgam and water are sometimes used for this purpose or concentrated hydriodic acid and phosphorus; (b) by passing hydrogen gas into the hydrocarbon in the presence of platinum black or colloidal palladium, which act as catalysts; (c) by passing a mixture of the vapour of the hydrocarbon and of hydrogen over finely-divided nickel (cf. Catalytic Hydrogenation, Chap. XLIX, A.).

Of the halogens chlorine combines most readily and iodine least readily; on the other hand, HI adds on more easily than HBr, and this more readily than HCl. It is obvious when the two addenda are different, e.g. HCl, i.e. H and Cl or HClO, i.e. HO and Cl, and the hydrocarbon is not symmetrical in structure that, theoretically, the addition can take place in two different ways. In reality, it is found that in the majority of cases the addition of halogen hydride is such that the halogen attaches itself to the carbon atom which is united to the smaller number of hydrogen atoms\*:



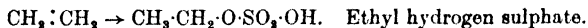
When aqueous solutions of bromine are used the reaction is not simply the addition of bromine and the formation of a dibromide. Part of the olefine combines with Br and OH, yielding a bromo-derivative of an alcohol (cf. Chap. LI, B.):



(Cf. *Reid* and others, J. C. S., 1917, 240; 1920, 359; 1922, 2552; 1928, 1488; *Baillman*, Rec. Trav., 1917, 313.) The addition of sodium bromide increases the amount of dibromide formed.

\* Cf. *Michael*, J. pr., 1888, [ii], 37, 524; 1903, 68, 487; B., 1906, 2138.

The reaction with sulphuric acid (concentrated or fuming) is complex. (Cf. *Brooks* and *Humphrey*, J. Am. C. S., 1918, 822). The products are polymerized olefines, alkyl hydrogen sulphates formed by the addition of H and O-SO<sub>2</sub>·OH to the hydrocarbons, and alcohols:

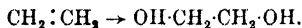


The tendency to form sulphates increases from ethylene to amylene, and then diminishes, whereas polymerization tends to increase with increase in molecular weight. For historical survey cf. C. I., 1935, 881.

(b) They readily polymerize, especially in presence of sulphuric acid or zinc chloride. Thus amylene, C<sub>5</sub>H<sub>10</sub>, in presence of sulphuric acid, yields the polymers C<sub>10</sub>H<sub>20</sub>, C<sub>15</sub>H<sub>30</sub>, and C<sub>20</sub>H<sub>40</sub>. Metals also tend to produce polymerization or isomerization (C. I., 1937, 323).

(c) Unlike the paraffins, they are readily oxidized by KMnO<sub>4</sub> or CrO<sub>3</sub>, but not by cold HNO<sub>3</sub>.

In this reaction, two hydroxyl groups are added to the molecule of the olefine if a dilute (1 per cent) solution of permanganate is used, and a dihydric alcohol (a glycol) is formed.



But if stronger solutions are used, or if chromic anhydride is employed, the molecule of the olefine is ruptured at the point where the double bond exists and a mixture of simpler acids or ketones is obtained. The readiness with which olefine compounds discharge the colour of acidified permanganate is frequently made use of as a qualitative test for such compounds, but is given by numerous other compounds, in fact by any organic compound which is readily oxidized, e.g. an aldehyde, an amine or a phenol.

*Nomenclature.*—Ethylene was first prepared by four Dutch chemists, who observed that it formed an oil with chlorine, hence they termed ethylene **olefiant gas**, and the name olefine has been given to the whole series of hydrocarbons.

The official names for the various olefines, as suggested by the Geneva Congress, are formed by replacing the last syllable "ane" of the paraffins by "ene". The position of the double bond is denoted by the number of the carbon atom from which it proceeds. In a branching chain the numbering is the same as in the case of the corresponding saturated hydrocarbons;

in a normal carbon chain it begins at the end carbon atom which is nearest to the double bond.

The following examples illustrate this system:

$\overset{1}{\text{CH}_3}\text{:}\overset{2}{\text{CH}}\text{:}\overset{3}{\text{CH}}\text{--}\overset{4}{\text{CH}_2}\text{--}\overset{5}{\text{CH}_3}$  is 2-pentene or  $\Delta^2$ -pentene, where  $\Delta$  denotes the double bond.

$\overset{1}{\text{CH}_3}\text{:}\overset{2}{\text{CH}}\text{:}\overset{3}{\text{C}}(\text{CH}_3)\text{--}\overset{4}{\text{CH}_2}\text{--}\overset{5}{\text{CH}_2}\text{--}\overset{6}{\text{CH}_3}$  is 3-methyl-2-hexene.

$\overset{1}{\text{CH}_3}\text{:}\overset{2}{\text{CH}}\text{:}\overset{3}{\text{C}}\begin{matrix} \nearrow \overset{4}{\text{CH}_2}\text{--}\overset{5}{\text{CH}_3} \\ \searrow \overset{3^1}{\text{CH}_2}\text{--}\overset{3^2}{\text{CH}_3} \end{matrix}$  is 3-ethyl-2-pentene.

$\overset{1}{\text{CH}_3}\text{:}\overset{2}{\text{CH}}\text{:}\overset{3}{\text{C}}\begin{matrix} \nearrow \overset{4}{\text{CH}}(\text{CH}_3)\text{--}\overset{5}{\text{CH}}\begin{matrix} \nearrow \overset{6}{\text{CH}_3} \\ \searrow \overset{7}{\text{CH}_3} \end{matrix} \\ \searrow \overset{8}{\text{CH}_3}\text{--}\overset{9}{\text{CH}_3} \end{matrix}$  is 4:5-dimethyl-3-ethyl-2-hexene.

$\overset{1}{\text{CH}_3}\text{:}\overset{2}{\text{CH}}\text{--}\overset{3}{\text{CH}_2}\text{--}\overset{4}{\text{C}}\begin{matrix} \nearrow \overset{5}{\text{CH}_2}\text{--}\overset{6}{\text{CH}_2}\text{--}\overset{7}{\text{CH}_3} \\ \searrow \overset{8}{\text{CH}_2}\text{--}\overset{9}{\text{CH}_3} \end{matrix}$  is 4-ethyl-4-propyl-1-heptene.

*Modes of formation.*—(a) Together with paraffins by the destructive distillation of many substances, such as wood, lignite, and coal, and also by the distillation of the higher paraffins (process of "cracking", p. 42); illuminating gas consequently contains the olefines  $\text{C}_2\text{H}_4$ ,  $\text{C}_3\text{H}_6$ ,  $\text{C}_4\text{H}_8$ , &c.

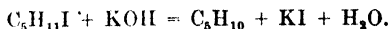
(b) By abstraction of water from the alcohols,  $\text{C}_n\text{H}_{2n+1}\text{OH}$ , by heating them with sulphuric acid, phosphorus pentoxide, zinc chloride, anhydrous formic acid, syrupy phosphoric acid, *p*-toluenesulphonic acid,  $\text{KHSO}_4$  or  $\text{Al}_2(\text{SO}_4)_3$ . With sulphuric acid, an alkyl-sulphuric acid, e.g. ethyl hydrogen sulphate,  $\text{C}_2\text{H}_5\text{O}\cdot\text{SO}_2\cdot\text{OH}$ , is first formed, and decomposes into alkylene and sulphuric acid. This method is especially applicable in the case of the lower homologues. Many alcohols yield olefines when heated alone, or with finely divided solids (Chap. XLIX, D.).

The silicols,  $\text{RCH}_2\cdot\text{SiH}_2\cdot\text{OH}$ , i.e. the silicon analogues of the alcohols do not lose water, forming compounds corresponding with the olefines.

The palmitic esters of the higher alcohols, when distilled under somewhat diminished pressure, yield palmitic acid and an olefine.

(c) By heating the halogen compounds  $\text{C}_n\text{H}_{2n+1}\text{X}$ , particularly the iodo- and bromo-compounds, with alcoholic potash,

or by passing their vapour over red-hot lime or hot oxide of lead, &c.; sometimes by simple distillation:



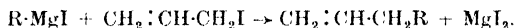
The molecule of halogen hydracid eliminated is formed from the halogen detached from the one carbon atom and the hydrogen from an adjacent. (Cf. also *Nef*, A., 1901, **318**, 3.)

(d) From the dihalides  $\text{C}_n\text{H}_{2n}\text{X}_2$ , particularly the dibromides, but only when the two bromine atoms are attached to adjacent C atoms, by treatment with zinc, magnesium, or zinc dust and alcohol:

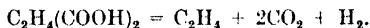


The reaction has proved of value in the preparation of pure olefines as the dibromides are usually solids and readily purified.

(e) By the action of an unsaturated alkylene iodide, e.g. allyl iodide on the alkyl magnesium iodide:

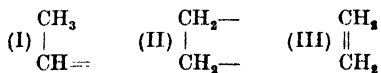


(f) By the electrolysis of potassium salts of dibasic acids of the succinic acid series; thus succinic acid itself yields ethylene:



The complex anion  $\text{O}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{O}$ , when discharged decomposes into ethylene and carbon dioxide.

*Constitution of the Olefines.*—For ethylene the following formulæ may be given:



In the formulæ I and II, two free carbon bonds or valencies are assumed in the ethylene molecule. Formula III follows from the assumption that the bonds which are not used up in attaching the hydrogen atoms to carbon are used in uniting the carbon atoms themselves.

Now the ethylene bromide which is formed by the addition of bromine to ethylene has, for reasons which will be given under that compound, the constitution  $\text{CH}_2\text{Br}\cdot\text{CH}_2\text{Br}$ , and likewise the compound obtained by the addition of  $\text{ClOH}$  (i.e.  $\text{Cl}$  and  $\text{OH}$ ), viz. glycol chlorhydrin, the constitution

$\text{CH}_2\text{Cl}\cdot\text{CH}_2\text{OH}$ ; consequently formula I, according to which these substances would have the constitutions  $\text{CH}_3\cdot\text{CHBr}_2$  and  $\text{CH}_3\cdot\text{CHCl}(\text{OH})$ , is excluded.

Formula III is more probable than formula II:

(a) Since methylene,  $\text{CH}_2\cdot$ , appears to be incapable of existence; all attempts to isolate it have yielded ethylene,  $\text{C}_2\text{H}_4$  (see below), so that free valencies attached to the carbon atom probably cannot exist. Cf., however, Chap. LII, B.

(b) Because the free affinities to be assumed according to II are never found singly (which should in that case be possible), but invariably in pairs only, and indeed only on neighbouring carbon atoms. This is proved from the constitution of the compounds obtained by the addition, for instance, of  $\text{Br}_2$ . Unsaturated compounds containing only one carbon atom, and unsaturated hydrocarbons containing an *odd* number of hydrogen atoms, are unknown.

It is therefore to be concluded that in ethylene and its homologues a double carbon bond, corresponding with formula III, exists.

By this term "double bond" is not, however, to be understood a closer or more intimate combination. The olefines, on the contrary, are more readily oxidized than the paraffins, being thereby attacked at the point of the double bond. Other properties, especially physical ones, also give indications that a double bond between two carbon atoms is more easily broken than a single one. (Cf. *Brühl*, A., 211, 162.)

1. **Methylene** (*Methene*),  $\text{CH}_2\cdot$ , does not exist. Numerous attempts to prepare it, e.g. by the withdrawal of hydrogen and chlorine from methyl chloride, or of iodine from methylene iodide, have invariably yielded ethylene, thus:



Here the two resulting  $\text{CH}_2$ -residues have united together, in the same way as the two methyl-groups coalesced to ethane (p. 37).

2. **Ethylene** (*Ethene*), olefiant gas,  $\text{CH}_2\text{:CH}_2$ .

This compound was discovered in 1795 by four Dutch chemists. Its formula was established by *Dalton*.

Illuminating gas generally contains 4 to 5 per cent of ethylene, and it is present in natural gas from oil wells and in the gases obtained by cracking oils (p. 42). For formation from elements see *Pring* and *Fairlie*, J. C. S., 1911, 1806. It is usually

prepared by heating alcohol with excess of concentrated sulphuric acid, with addition of sand or anhydrous aluminium sulphate, a mixture of equal portions of the two liquids being subsequently dropped into the evolution flask; sulphur dioxide, &c., are produced at the same time by secondary reactions. A better method is to heat alcohol with syrupy phosphoric acid at  $200^{\circ}$  (*Newth*), or to pass alcohol over anhydrous alum. It is further formed by heating ethylidene chloride,  $\text{CH}_3\cdot\text{CHCl}_2$ , with sodium, or ethylene bromide with zinc.

It may be liquefied at  $0^{\circ}$  under a pressure of 44 atmos., is very slightly soluble in water and alcohol; burns with a luminous flame, and forms an explosive mixture with oxygen. When rapidly mixed with two volumes of chlorine and set fire to, it burns with a dark-red flame, with formation of hydrochloric acid and deposition of much soot. It is converted at a red heat into methane,  $\text{CH}_4$ , ethane,  $\text{C}_2\text{H}_6$ , acetylene,  $\text{C}_2\text{H}_2$ , &c., with separation of carbon. It combines with hydrogen in presence of spongy platinum to ethane,  $\text{C}_2\text{H}_6$ .

3. **Propylene** (*Propene*),  $\text{C}_3\text{H}_6$ ,  $\text{CH}_2\text{:CH}\cdot\text{CH}_3$ . Only one olefine,  $\text{C}_3\text{H}_6$ , is theoretically possible and only one is known, viz. methylethylene. It can be prepared from isopropyl iodide and caustic potash, or by heating glycerol with zinc dust. It is isomeric with trimethylene (see Polymethylenes).

4. **Butylene**,  $\text{C}_4\text{H}_8$ . Three butylenes are possible according to theory, and three are known. All of them are gaseous, their boiling-points lying between  $-6^{\circ}$  and  $+3^{\circ}$ . Butylene and pseudo-butylene are derived from normal butane, and isobutylene from isobutane, since they severally combine with  $\text{H}_2$  to form these hydrocarbons. The first,  $\alpha$ -butylene, is prepared from normal; the second,  $\beta$ -butylene, from secondary; and the third,  $\gamma$ -butylene, from tertiary butyl iodide, by the action of caustic potash upon these; the last can also be obtained from isobutyl alcohol and sulphuric acid. The isomerism of the two butylenes derived from normal butane is explained by the assumption of a double bond at different points, thus:



Isobutylene has the formula  $(\text{CH}_3)_2\text{C}\text{:CH}_2$  (*methylpropene*). The behaviour of these isomers upon oxidation is in accordance with the above formula, the oxidation always taking place at the point of the double bond.

The butylenes are isomeric with tetra-methylene (*cyclobutane*, see Polymethylenes).

5. **Amylene**,  $C_5H_{10}$ . A large number of isomeric amylenes are known, among them being **Amylene** (b.-pt.  $35^\circ$ ), which is obtained, together with an isomer, Iso-amylene, by heating ordinary amyl alcohol with chloride of zinc. For it the constitutional formula  $(CH_3)_2C:CH\cdot CH_3$  (trimethylethylene) is assumed. This is known in the pure form under the name of "pental".

The higher Olefines of normal constitution, with 12, 14, 16, and 18 atoms of carbon, have been prepared by *Krafft* according to method *b*.

**Cerotene** and **Melene** (m.-pt.  $62^\circ$ ) are obtained by the distillation of Chinese wax and bees'-wax respectively. They are like paraffin in appearance, and are only sparingly soluble in alcohol.

### C. Hydrocarbons, $C_nH_{2n-2}$ : Acetylene Series

The hydrocarbons of this series again differ from those of the preceding by containing two atoms of hydrogen less. In physical properties they closely resemble both the latter and those of the methane series; thus the lowest members up to  $C_4H_6$  are gaseous, the middle ones liquid, and the highest solid, and in their melting- and boiling-points they do not differ to any extent from those of the other series with an equal number of carbon atoms. The specific gravities of the normal hydrocarbons  $C_{12}$ ,  $C_{14}$ ,  $C_{16}$ , and  $C_{18}$ , at the melting-point, gradually approach with increasing carbon to a definite limit (0.80), and are somewhat higher than those of the corresponding members of the ethylene series throughout.

*Constitution*.—Upon grounds similar to those which have already been explained under ethylene, the constitutional formula for acetylene,  $C_2H_2$ , is assumed to be  $CH:CH$ , according to which the carbon atoms are joined together by a triple bond.

For a compound  $C_3H_4$ , two constitutional formulæ are possible:  $CH:C\cdot CH_3$  (allylene) and  $CH_2:C:CH_2$  (allene).

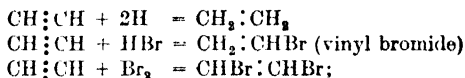
As a matter of fact, two hydrocarbons  $C_3H_4$  do exist, only one of which, allylene, yields metallic compounds. It is therefore to be considered the true homologue of acetylene, containing a triple bond, according to the first of the two above formulæ, while to allene the second formula, with the two double bonds,



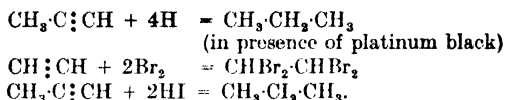
is to be ascribed. The constitution of the tetrabromopropanes, which are formed from these by the addition of bromine, agrees with this conception.

In their chemical relations the acetylenes stand nearer to the olefines than to the paraffins, in so far that they are unsaturated and therefore capable of forming additive products.

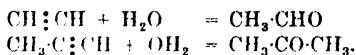
1. A molecule of an acetylene can combine either (a) with two atoms of hydrogen or halogen, or with one molecule of halogen hydride, to olefines or their substitution products, thus:



or (b) with four atoms of hydrogen or halogen, or two molecules of halogen hydride, to paraffins or paraffin substitution products, thus:



Like many of the olefines, various members of this series combine with water under the influence of dilute acids, thus allylene,  $\text{C}_3\text{H}_4$ , gives acetone,  $\text{C}_3\text{H}_6\text{O}$ ; and acetylene,  $\text{C}_2\text{H}_2$ , gives crotonic aldehyde, with intermediate formation of acetic aldehyde. The combination with water may be accomplished (a) by the action of sulphuric acid when, as in the case of the olefines, alkyl hydrogen sulphates are formed as intermediate products; at  $0^\circ$  under pressure ethylene gives a nearly theoretical yield of ethyl hydrogen sulphate; (b) by means of mercuric chloride solution or of mercury and acids; or (c) by directly heating the hydrocarbon with water at  $300^\circ$  in sealed tubes.



2. Many of the acetylene hydrocarbons are readily polymerized; thus, acetylene is transformed into benzene when led through a red-hot glass tube. This is an important synthesis of benzene:  $3\text{C}_2\text{H}_2 = \text{C}_6\text{H}_6$ . At the same time the compounds  $\text{C}_8\text{H}_8$ ,  $\text{C}_{10}\text{H}_8$ , &c., are formed. Similarly allylene,  $\text{C}_3\text{H}_4$ , gives mesitylene,  $\text{C}_9\text{H}_{12}$ , in contact with sulphuric acid and a little water. (See Benzene Derivatives.)

3. Acetylene and some of its homologues react in a characteristic manner with an ammoniacal solution of cuprous or argentic oxide, to form reddish-brown or yellow-white precipitates, e.g.  $\text{CCu}:\text{CCu}$ ;  $\text{CAg}:\text{CAg}$ ;  $\text{CH}_3:\text{C}:\text{CAg}$ , &c., which are explosive, and which are decomposed by acids, such as  $\text{HCl}$ , with regeneration of the hydrocarbon. The first products formed appear to be additive compounds, e.g.  $\text{C}_2\text{H}_2$ ,  $\text{CuCl}$ , and these then yield the substituted derivatives.

The mercuric compounds  $\text{Hg}(\text{C}:\text{CR})_2$  obtained by the action of  $\text{K}_2\text{HgI}_4$  on the hydrocarbons have definite melting-points, and are of value in characterizing monoalkyl acetylenes (J. A. C. S., 1933, 3453, 4206). Acetylenes also react with the compounds  $\text{R}\cdot\text{Hg}\cdot\text{Br}$ , analogous to *Grignard* reagents (Chap. IV, G.), e.g. acetylene with  $\text{R}\cdot\text{HgI}$  gives crystalline derivatives  $\text{R}\cdot\text{HgC}:\text{CHgR}$ , and monoalkyl acetylenes with *Grignard* compounds give the compounds  $\text{R}\cdot\text{C}:\text{CMgBr}$ , which are not so reactive as normal *Grignard* reagents. An additive compound  $\text{C}_2\text{H}_2\cdot\text{HgCl}_2$  is also known.

The hydrogen of acetylene is replaced by sodium when the hydrocarbon is heated with sodium or sodamide, and the compounds  $\text{C}_2\text{HNa}$  and  $\text{C}_2\text{Na}_2$  are formed. These are decomposed by water or acids with evolution of acetylene.

(For syntheses with the aid of acetylene, see Chap. LI, F.)

All the hydrocarbons  $\text{C}_n\text{H}_{2n-2}$  do not, however, give such metallic compounds, but only the monoalkyl derivatives  $\text{R}\cdot\text{C}:\text{CH}$ . Hydrocarbons such as allene,  $\text{CH}_2:\text{C}:\text{CH}_2$ , which do not contain a triple bond, and even acetylene compounds such as  $\text{CH}_3:\text{C}:\text{C}\cdot\text{CH}_3$ , where no hydrogen atoms are attached to the C atoms between which the triple bond is supposed to exist, do not yield these metallic derivatives.

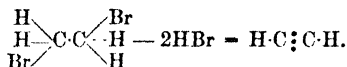
In the case of higher homologues, isomerism may be due either to the difference in position of the triple carbon bond in the molecule, or to the presence and different positions of two double bonds. The constitution of a compound is fixed by its behaviour or otherwise of metallic derivatives, and by its behaviour upon oxidation. (See Oxidation of the Butylenes, p. 52.)

The official name of the acetylene homologues proper, with a triple carbon-linking, ends in "ine"; that of the isomeric hydrocarbons, with two double bonds, in "diene".

*Formation*.—1. They are obtained, together with the hydrocarbons already described, by the distillation of wood, lignite,

coal, &c.; thus illuminating gas contains acetylene, allylene, and crotonylene.

2. By treating the halide, preferably the bromine, compounds,  $C_nH_{2n}X_2$  and  $C_nH_{2n-1}X$  with alcoholic potash or sodium ethoxide ( $C_2H_5ONa$ ):



With alcoholic potash, even when excess is used, the reaction tends to stop at the first stage, and a brominated olefine is formed, e.g. vinyl bromide (p. 70) from ethylene dibromide; with sodium ethoxide the elimination of hydrogen bromide proceeds more readily.

Unsaturated alcohols,  $C_nH_{2n-1}\cdot OH$ , by the elimination of water, yield acetylenes.

3. By the electrolysis of potassium salts of the acids of the fumaric acid series (*Kekulé*).

4. Certain dialkyl acetylenes,  $R\cdot C\text{:}C\cdot CH_3$ , when heated with sodium, give the sodium compounds of the isomers,  $R\cdot CH_2\cdot C\text{:}CH$ ; but when the latter are warmed with alcoholic potash, the opposite reaction takes place.

**Acetylene** (*Ethine*),  $C_2H_2$ , was first obtained impure by *E. Davy* from calcium carbide in 1839, and pure by *Berthelot* in 1849. Coal gas contains 0.06 per cent. It is synthesized from its elements, when an electric arc is caused to pass between two carbon poles in an atmosphere of hydrogen (*Berthelot*), but other hydrocarbons are formed at the same time (*Bone and Jerdan*, J. C. S., 1901, 1042; cf. also *Hutton and Pring*, 1906, 1591). It may be obtained from ethylene bromide and sodium ethoxide solution; also by the incomplete combustion of many carbon compounds, for instance, when the gas in a *Bunsen* lamp burns at the base; and from ethane, ethylene, and methane at a red heat, or by the action of the induction spark. (See pp. 35 and 52.) The simplest method of preparation is by the action of water on calcium carbide, the water being allowed to drop gradually on to the carbide:



An alternative method is from industrial gases such as coke oven gases or low temperature carbonization gases. After removal of CO the residue—mainly  $H_2$  and  $CH_4$ —is momen-

tarily heated to a high temperature under reduced pressure and suddenly cooled.

It becomes liquid at  $1^{\circ}$  under a pressure of 48 atmospheres. When stored as liquid or a gas under pressure it is liable to explode. Its heat of formation,  $-54.8$  cal., indicates its instability and it is usually stored in cylinders containing porous material and a little acetone under pressure of 10 atmos. It burns with a luminous and very sooty flame, and has a peculiar disagreeable smell. Its flame has a high illuminating power when burnt in specially-constructed burners, and is largely made use of as an illuminating agent. It dissolves in its own volume of water, and in six times its volume of alcohol; is poisonous, combining with the hæmoglobin of the blood. It is decomposed into its elements with detonation by explosive fulminate of silver, and also by the electric spark. It combines with hydrogen to ethane, when heated with the latter in presence of platinum black, or to ethylene, upon treating its copper compound with zinc and ammonia. A mixture of acetylene and oxygen explodes violently when a light is applied to it. Chromic acid oxidizes acetylene to acetic acid, and permanganate of potash to oxalic acid. It combines with nitrogen under the influence of the induction spark to hydrocyanic acid (see this), and detonates upon being mixed with chlorine, but additive products, e.g.  $C_2H_2Cl_2$ , can, however, be prepared. As little as .005 milligramme of it can be detected by the formation of the dark-red copper compound  $C_2Cu_2$ . This latter explodes when struck, or when heated to a little over  $100^{\circ}$ .

**Allylene** (*Propine*),  $CH_3 \cdot C : CH$ , prepared from propylene bromide,  $CH_3 \cdot CHBr \cdot CH_2Br$ , resembles acetylene, and the isomeric.

**Allene** (*Propadiene*),  $CH_2 : C : CH_2$ , is obtained by the electrolysis of itaconic acid.

**Diallyl** (*Hexa-1 : 5-diene*),  $CH_2 : CH \cdot CH_2 \cdot CH_2 \cdot CH : CH_2$ , is obtained from allyl iodide,  $CH_2 : CH \cdot CH_2I$ , and Na, Zn, or Cu.

Isomeric with these hydrocarbons are certain hydro-derivatives of aromatic hydrocarbons, e.g. tetrahydrobenzene,  $C_6H_{10}$ ; decahydronaphthalene,  $C_{10}H_{18}$ . (See Aromatic Compounds.)

Certain di-olefines are of importance from their relationship to rubber (cf. open chain terpenes, Chap. LVII, A., and Rubber, Chap. LXI, B.).

### D. Hydrocarbons $C_nH_{2n-6}$

**Di-acetylene** (*Butadiene*),  $C_4H_2$ , or  $CH:C:C:CH$ . This is prepared by heating the ammonium salt of diacetylene-dicarboxylic acid (see this) with ammoniacal copper solution, whereby it is transformed into the cuprous compound of diacetylene, and then warming this with potassium cyanide. It is a gas of a peculiar odour, which yields a violet-red copper compound and a yellow silver one, the latter exploding upon being rubbed, even when moist. (*Baeyer*, B., 1885, 2269.)

**Di-propargyl** (*1:5-Hexadiene*),  $C_6H_6$ , or  $CH:C\cdot CH_2\cdot CH_2\cdot C:CH$ , is obtained by the conversion of diallyl into its tetra-bromide, and the subsequent elimination of four molecules of hydrogen bromide from each molecule of the tetra-bromide; b.-pt.  $85^\circ$ . It gives copper and silver compounds, and takes up eight atoms of bromine, &c. It possesses an especial interest, as it is isomeric with benzene. Another isomeride is *2:4-Hexadiene*,  $CH_3\cdot C:C:C:C\cdot CH_3$ .

An interesting compound is vinylacetylene,  $CH:C\cdot CH:CH_2$ , containing a double and a triple linking. It is formed from butadiene dibromide by the process of exhaustive methylation (cf. Chap. LVIII).

## II. HALIDE SUBSTITUTION PRODUCTS OF THE HYDROCARBONS

### A. Halogen Derivatives of the Paraffins

These are to be regarded as paraffin hydrocarbons in which one or more hydrogen atoms have become replaced by one or more halogen atoms.

**General Properties.**—Only a few of these compounds, e.g.  $CH_3Cl$ ,  $C_2H_5Cl$ , and  $CH_3Br$ , are gaseous at the ordinary temperature; most of them are liquid, and those with a very large number of carbon atoms in the molecule solid, e.g. cetyl iodide,  $C_{16}H_{33}I$ . The introduction of a halogen atom in any hydrocarbon in place of an atom of hydrogen always tends to

raise the boiling-point; the introduction of iodine has the most marked effect, and chlorine the least (cf. table, p. 60). Under comparable conditions, the boiling-points of the iodides lie, for each atom of halogen, about  $50^{\circ}$  ( $40^{\circ}$ – $60^{\circ}$ ), and those of the bromides about  $22^{\circ}$  ( $20^{\circ}$ – $24^{\circ}$ ), above those of the chlorides, so that the graphs obtained by plotting boiling-points against number of C atoms in the chain form practically parallel curves. Those which contain a large number of halogen atoms, e.g.  $\text{CCl}_4$ ,  $\text{C}_2\text{Cl}_6$ , are solid.

The lowest members of the series have, in the liquid form, at first a higher specific gravity than water, e.g.  $\text{CH}_3\text{I}$ , sp. gr. 2.2,  $\text{C}_2\text{H}_5\text{Br}$ , sp. gr. 1.47. With an increasing number of carbon atoms, however, the influence of the halogen diminishes, and they become lighter than water.

The halogen substitution products of the hydrocarbons are very sparingly soluble in water, but readily in, and therefore miscible to any extent with, alcohol or ether; they also dissolve in glacial acetic acid, and these solutions are only feeble electrolytes. They often possess a sweet ethereal odour, but this becomes less marked with diminishing volatility. Most of them are combustible; thus methyl and ethyl chloride burn with a green-bordered flame, while ethyl iodide and chloroform can only be set fire to with difficulty. Many members of the series containing one or two atoms of carbon produce insensibility and unconsciousness when inhaled, e.g.  $\text{CHCl}_3$ ,  $\text{C}_2\text{H}_3\text{Cl}_3$ ,  $\text{C}_2\text{H}_5\text{Br}$ , and  $\text{C}_2\text{HCl}_5$ . The liquid iodine derivatives are readily decomposed, and on exposure to light turn deep-brown in colour, owing to the liberation of free iodine, e.g. ethyl iodide liberates iodine and gives  $\text{C}_4\text{H}_{10}$ .

In all these compounds the halogen is more firmly bound than in inorganic salts, so that, for instance, when silver nitrate is added to an aqueous solution of a chlorine compound, e.g. chloroform, it causes no precipitation of  $\text{AgCl}$ . Nevertheless, the halogen is in most cases readily exchangeable for other elements or groups, a circumstance of the utmost importance for many organic reactions. This is especially true for the iodine and bromine compounds, which react more readily than the chlorides, and, on account of their lesser volatility, are easier to work with; thus  $\text{C}_2\text{H}_5\text{Br}$  reacts with  $\text{AgNO}_3$  at the boiling temperature, and  $\text{C}_2\text{H}_5\text{I}$  in the cold.

In all these halogen compounds the halogen can be again replaced by hydrogen by inverse substitution, e.g. by sodium

amalgam, by zinc dust and hydrochloric or acetic acid, or by heating with hydriodic acid. (See p. 32.)

Of fluorine compounds, comparatively few are known:  $\text{CH}_3\text{F}$  and  $\text{C}_2\text{H}_5\text{F}$  are gases.

*Nomenclature.*—The best system of nomenclature is to regard them as derived from the corresponding hydrocarbons, e.g.  $\text{CHCl}_3$  trichloro-methane,  $\text{CH}_3\text{I}$  mono-iodo-methane, and if necessary to indicate the carbon atoms to which the halogen radicals are attached, e.g.  $\text{CH}_2\text{Cl}\cdot\text{CH}_2\text{Cl}$  1:2-dichloro-ethane,\*  $\text{CH}_3\cdot\text{CHBr}_2$  1:1-dibromo-ethane,  $\text{CH}_2\text{Br}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{Br}$  1:3-dibromo-propane,  $\text{CH}_3\cdot\text{CH}(\text{CH}_3)\cdot\text{CHBr}\cdot\text{CH}_2\cdot\text{CH}_2\text{Br}$  2-methyl-3:5-dibromo-pentane.

*Formation.*—1. By **Substitution.**—*Chlorination and Bromination.* Chlorine and bromine act for the most part as direct substituents (see p. 31). With the gaseous hydrocarbons their action even in the cold is an extremely energetic one (e.g. chlorine mixed with methane easily causes an explosion, so that dilution with  $\text{CO}_2$  is necessary); the higher members require to be heated.

## HALOGEN SUBSTITUTION PRODUCTS

### Saturated Compounds

#### (a) Mono-substituted Derivatives.

	Chloride		Bromide		Iodide	
	B.-p.	Sp. gr.	B.-p.	Sp. gr.	B.-p.	Sp. gr.
Methyl ..	-23.7°	0.952	+4.5°	1.732	+45°	2.293
Ethyl ..	+12.2	0.918	38.4	1.468	72.3	1.944
<i>n</i> -Propyl ..	46.5	0.912	71	1.383	102.5	1.786
<i>Iso</i> -Propyl ..	36.5	0.882	60	1.340	89	1.744
<i>n</i> -Butyl ..	78	0.907	101	1.305	130	1.643
<i>n</i> -Pentyl ..	105.7	0.883	128	1.223	156	1.517
<i>n</i> -Hexyl ..	134	0.872	156	1.173	180	1.441
<i>n</i> -Heptyl ..	159.5	0.881	179	1.133	204	1.401
<i>n</i> -Octyl ..	184.6	0.879	204	1.116	225	1.341

#### (b) Di-substituted Derivatives.

	Chloride		Bromide		Iodide	
	B.-p.	Sp. gr.	B.-p.	Sp. gr.	B.-p.	Sp. gr.
Methylene ..	42°	1.337	97°	2.498	180°	3.292
Ethylene ..	84	1.260	131	2.189	solid; m.-p.	81-82
Ethylidene ..	58	1.189	110	2.080	178	2.84

\* This is identical with ethylene dichloride. It should never be termed dichlorethylene, which is  $\text{CHCl}:\text{CHCl}$ , a substitution product of ethylene.

(c) *Tri-substituted Derivatives.*

CHX <sub>3</sub> .. ..	Chloroform b.-p. 61°	Bromoform b.-p. 151°	Iodoform melts at 119° sublimes
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 (d) *Tetra-substituted Derivatives.*

Carbon tetra- CX <sub>4</sub> .. ..	Chloride 76°	Bromide m.p. 92°; b.-p. 189°
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## Unsaturated Compounds

	Chloride	Bromide	Iodide
Vinyl, CH <sub>2</sub> :CHX .. ..	- 18°	+ 16°	56°
Allyl, CH <sub>2</sub> :CH-CH <sub>2</sub> X ..	45°	71°	103°

Trichlorethylene boils at 88°, tetrachlorethylene at 121°. Monochlor- and monobrom-acetylene are gaseous.

Compounds of the type CCl<sub>3</sub>Br, CCl<sub>2</sub>Br<sub>2</sub>, CCl<sub>2</sub>I<sub>2</sub>, &c., are also known.

The first halogen atom enters most easily into the compound, the substitution becoming more difficult as the number of those atoms present increases. In the case of the higher hydrocarbons, two isomeric mono-substitution products are usually formed. The action of the halogens is further facilitated by sunlight, and by the presence of iodine, this latter acting as a carrier of chlorine by the alternate formation of ICl<sub>3</sub> and ICl, thus: ICl<sub>3</sub> = ICl + 2Cl. Antimony pentachloride and ferric chloride act in the same way (and also for brominating and iodating—B., 1885, 2017; A., 231, 195); iron wire is especially useful in brominating (B., 1891, 4249). When complete chlorination is required, the substance in question is repeatedly saturated with chlorine in presence of iodine, and heated in a tube to a high temperature.

From methane are formed the whole series of substitution products up to CCl<sub>4</sub>.

Ethane first yields ethyl chloride, C<sub>2</sub>H<sub>5</sub>Cl, then ethylidene chloride, C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub>, and so on up to C<sub>2</sub>Cl<sub>6</sub>.

From propane is first produced normal propyl chloride, C<sub>3</sub>H<sub>7</sub>Cl, and finally C<sub>3</sub>Cl<sub>8</sub>. The latter decomposes, upon vigorous chlorination, first into C<sub>2</sub>Cl<sub>6</sub> and CCl<sub>4</sub>, and the perchloro-ethane subsequently into two molecules CCl<sub>4</sub>. On chlorinating butane and the higher hydrocarbons strongly, an analogous splitting up of the molecule is effected. Strong



chlorination or bromination readily gives rise at the same time to hexachloro- or hexabromo-benzene.

Iodine seldom acts as a direct substituent, since by this reaction hydrogen iodide would be formed, which would then reduce the iodine compound back to the hydrocarbon. (See p. 32.) To induce the action, therefore, the HI formed must be removed by  $\text{HIO}_3$  or  $\text{HgO}$ . The iodine substitution products of the hydrocarbons are usually prepared indirectly (according to 2 or 3.)

2. From **Unsaturated Hydrocarbons**. These combine readily with halogen or halogen hydride. (See p. 46.)

Ethylene gives with hydrochloric, hydrobromic, and hydriodic acids, ethyl chloride, &c., i.e. mono-substitution products of ethane; with chlorine, &c., it gives di-substitution products.

The compound  $\text{C}_2\text{H}_4\text{Cl}_2$ , obtained by the action of chlorine, is called ethylene chloride, has the constitutional formula  $\text{CH}_2\text{Cl}\cdot\text{CH}_2\text{Cl}$ , and is isomeric with the ethylidene chloride  $\text{CH}_3\cdot\text{CHCl}_2$ , obtained by the chlorination of  $\text{C}_2\text{H}_5\text{Cl}$ . (For an explanation of this isomerism, see p. 67.)

Propylene combines with hydriodic acid to isopropyl iodide,  $\text{C}_3\text{H}_7\text{I}$ , which is reconverted into propylene by elimination of HI. But the same propylene results from a compound isomeric with isopropyl iodide, viz. normal propyl iodide (and also, of course, from the above-mentioned normal propyl chloride) by the elimination of hydrogen iodide (or chloride), so that by this reaction normal propyl iodide can be transformed into isopropyl iodide. (See p. 65.) From the three butylenes there are formed two butyl iodides, viz. secondary and tertiary, which, as well as the two other existing butyl iodides, yield these butylenes again with alcoholic potash; in this way the two last-mentioned butyl iodides are convertible into their isomers, the two first (see p. 65).

A study of the constitution of the compounds formed, shows that in these additive reactions the *halogen invariably attaches itself to that carbon atom with which are combined the least number of hydrogen atoms* (cf. Chap. LI), e.g.

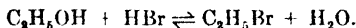


from  $\text{C}_3\text{H}_7\text{X}$  onwards, therefore, we obtain only "secondary" and "tertiary" \* compounds.

\* The names "primary", "secondary", and "tertiary" compounds are founded upon those of the alcohols—primary, secondary, and tertiary—in question, from which they can be prepared according to method 3, a.

### 3. From Compounds containing oxygen.

(a) From the alcohols  $C_nH_{2n+1}OH$ . In these the OH is readily exchangeable for chlorine, bromine, or iodine by the action of halogen hydride, thus:

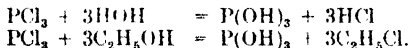


In such exchange the halogen takes the place of the hydroxyl, so that the constitution of the halide product corresponds with that of the alcohol used.

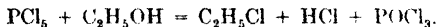
These reactions are reversible or balanced, and a state of equilibrium is reached; according to the law of mass action, it is therefore necessary either to use a large excess of halogen hydride, or to remove the water formed, by sulphuric acid, zinc chloride, &c.

Methyl and ethyl chlorides are easily prepared by distilling the corresponding alcohol with common salt and sulphuric acid, or by leading hydrogen chloride into the warm alcohol containing half its weight of zinc chloride in solution (*Groves*).

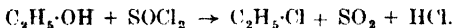
The chlorides of phosphorus react in much the same way with alcohols as with water, thus:



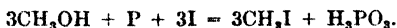
Phosphorus pentachloride is most frequently used for this purpose,



Phosphorus oxychloride itself is also sometimes employed. The use of phosphorus chlorides is not common, as complex phosphorus compounds are formed, and thionyl chloride  $SOCl_2$  often gives better yields (*M'Kenzie* and others, *J. C. S.*, 1913, 698; *J. Biol. C.*, 1924, 551).



Of especial importance here is the application of the halogen compounds of phosphorus in the production of bromine and iodine compounds. The former need not be prepared beforehand, the end being achieved by gradually bringing phosphorus and iodine or bromine together in presence of the alcohol:



This is the method usually employed for the preparation of methyl and ethyl iodides.

(b) The halogen derivatives may also be prepared from polyhydric alcohols, e.g. trichlorhydrin,  $C_3H_5Cl_3$ , from glycerol,  $C_3H_5(OH)_3$ , and  $PCl_5$ ; isopropyl iodide,  $C_3H_7I$ , or allyl iodide,  $C_3H_5I$ , from glycerol and  $PI_3$  according to the conditions of the experiment (see p. 65); hexyl iodide,  $C_6H_{13}I$ , from mannitol,  $C_6H_8(OH)_6$  and  $HI$ , the latter acting here as a reducing agent also.

(c) From aldehydes and ketones (see these), dichloro-substitution products are formed by the action of  $PCl_5$ , e.g. ethylene chloride,  $CH_3\cdot CHCl_2$ , from aldehyde,  $CH_3\cdot CH:O$ ; acetone chloride,  $CH_3\cdot CCl_2\cdot CH_3$ , from acetone  $CH_3\cdot CO\cdot CH_3$ .

4. Chlorine and bromine compounds are frequently formed from the corresponding iodine or bromine ones by direct exchange, e.g. isopropyl bromide from the iodide, or methylene bromide from methylene iodide; (also by treatment with mercuric chloride, stannic chloride, or fuming hydrochloric acid). Conversely the chlorides and bromides may be transformed into the iodides by heating with sodium iodide in alcoholic or better acetone solution (B., 1910, 1528), dry calcium iodide, or with fuming hydriodic acid. Fluorides are often formed from iodides and silver fluoride at room temperature.

### MONO-SUBSTITUTION PRODUCTS

The **methyl** and **ethyl** compounds are usually obtained from the corresponding alcohols by one or other of the following methods: (a) Grove's method (p. 63); (b) action of concentrated sulphuric acid and sodium halide; (c) phosphorus and halogen.

**Methyl chloride** is often obtained by heating trimethylamine hydrochloride at  $360^\circ$ . Methyl chloride is used for the production of artificial cold, for extracting perfumes from flowers, and for methylating dyes in the colour industry. It burns with a green-bordered flame. The bromide is utilized as a fire extinguisher.

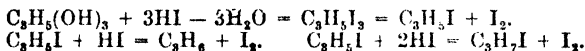
**Ethyl Fluoride**,  $C_2H_5F$ . A gas of ethereal odour, which liquefies at  $-48^\circ$ ; it burns with a blue flame, and does not attack glass.

Ethyl chloride is manufactured by passing  $HCl$  gas and ethyl alcohol vapour over activated charcoal and phosphoric acid at  $280-300^\circ$ . Yield 95 per cent. It is used as a local anæsthetic.

Each **Propyl halide**,  $C_3H_7X$ , exists in two isomeric forms, the normal propyl and the isopropyl compounds, the former boiling at a somewhat higher temperature than the latter. To the normal compounds the constitutional formula  $CH_3 \cdot CH_2 \cdot CH_2X$  is ascribed, and to the iso-compounds the formula  $CH_3 \cdot CHX \cdot CH_3$ , since they are derivable respectively from normal propyl alcohol and from isopropyl alcohol or acetone, the constitutions of which can readily be determined.

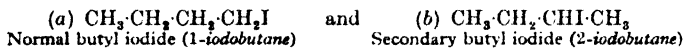
According to theory only these two cases are possible, since propane,  $CH_3 \cdot CH_2 \cdot CH_3$ , contains but two types of hydrogen atoms, viz.: (1) six combined with the end carbon atoms, and (2) two combined with the middle ones. For the transformation of the normal into the iso-compounds, see p. 62.

**Isopropyl iodide**, 2-iodopropane, is prepared from glycerol, phosphorus, iodine, and water (see p. 64); allyl iodide (p. 71) is formed as intermediate product, and at the same time some propylene (p. 52):

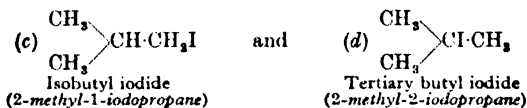


Each **Butyl-halide compound**,  $C_4H_9X$ , is known in four isomeric forms, which differ from one another in boiling-point (up to  $30^\circ$ ).

Four isomers are theoretically possible; thus from normal butane,  $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_3$ , are derived:



according to whether a "terminal" or "central" hydrogen atom is replaced; similarly from trimethylmethane,  $CH(CH_3)_3$ , are derived:



The constitutions of these four compounds follow from those of the four corresponding butyl alcohols (p. 74), from which they can be prepared by the action of halogen hydride.

Isobutyl bromide changes into the tertiary compound when heated at  $230^\circ$ – $240^\circ$ , and the reverse change also occurs, so that the final product is an equilibrium mixture of the two isomers, containing 80 per cent of the tertiary, and the rate of change

largely depends upon the presence of impurities (*Michael* and others, A., 1912, **393**, 81; J. A. C. S., 1916, 653; *Brunel*, 1917, 1978; cf. also C. R., 1913, **156**, 659).

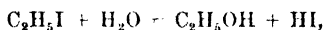
The Isobutyl compounds are the easiest to prepare (from isobutyl alcohol). The Tertiary readily react with  $H_2O$  to form the alcohol and halogen hydride, this taking place even in the cold in the case of the iodide.

These mono-halogen derivatives are one of the most important groups of reagents employed by the organic chemist, on account of the readiness with which the halogen atoms may be replaced by other radicals.

Some of the more characteristic reactions are;

1. Replacement of halogen by hydrogen. Inverse substitution (see p. 32).

2. Replacement of halogen by OH (hydroxyl) (p. 77),



generally by the aid of aqueous alkali, moist silver oxide, or lead oxide and water.

3. Alkalis in alcoholic solution, or alcoholic solutions of sodium methoxide ( $CH_3ONa$ ) or sodium ethoxide ( $C_2H_5ONa$ ), as a rule, eliminate halogen hydrides, and yield olefines,  $CH_2I \cdot CH_3 - HI = CH_2:CH_3$ . It is necessary that the halogen derivative contain at least two carbon atoms, and that a hydrogen atom should be attached to a carbon atom adjacent to the one to which the halogen is united.

Tertiary iodides react most readily, thus tertiary-butyl iodide  $C(CH_3)_3I$  with alkali, with ammonia or with silver cyanide does not yield  $\cdot OH$ ,  $\cdot NH_2$  or  $\cdot CN$  derivatives, but the butylene  $C(CH_3)_2 \cdot CH_2$ .

4. The halogen may be replaced by the amino group  $\cdot NH_2$  by the aid of ammonia under pressure, by the nitro group

$\cdot N \begin{smallmatrix} \nearrow O \\ \searrow O \end{smallmatrix}$  or nitrite radical  $\cdot O \cdot N : O$  (p. 104), and by the nitrile

radical  $\cdot C : N$  (p. 111).

For their use as synthetical reagents, see pp. 139, 261, 272.

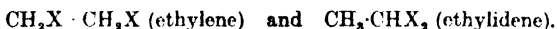
The reactivity of a halogen compound depends upon several factors: (1) The nature of the halogen atom; as a rule I reacts most readily and F least readily. (2) The nature of the adjacent groups, e.g. tertiary butyl iodide is more reactive than the *n*-compound. In  $CH_2Br \cdot CH_2 \cdot CH_2Br$  both bromine atoms are

readily replaced by OH or CN, whereas in  $\text{CH}_2\text{Br}\cdot\text{CR}_2\cdot\text{CH}_2\text{Br}$  it is difficult to replace the bromines. (3) The type of linking in the carbon chain. Thus a double link in the  $\alpha\beta$  position with respect to the halogen renders the halogen more difficult to displace. (4) The nature of the reagent employed. Thus a methyl halide is more reactive to sodium phenoxide,  $\text{C}_6\text{H}_5\text{ONa}$ , than is an ethyl halide, but with  $\text{AgNO}_2$  ethyl iodide reacts more readily than methyl iodide.

## DI-SUBSTITUTION PRODUCTS

**Methylene chloride**,  $\text{CH}_2\text{Cl}_2$ , **Methylene bromide**,  $\text{CH}_2\text{Br}_2$ , and **Methylene iodide**,  $\text{CH}_2\text{I}_2$ , are colourless liquids which are obtained either from the tri-halide substitution products by inverse substitution, or from the mono-substitution products by the introduction of more halogen.

The compounds  $\text{C}_2\text{H}_4\text{X}_2$  exist in two isomeric forms, viz.:



The **ethylene** dichloride and dibromide are formed by the addition of halogen to ethylene or by the action of hydrogen halides or phosphorus halides or glycol (cf. Chap. VIII, A.). With alcoholic potash or sodium ethoxide they yield, by the elimination of  $2\text{HX}$ , acetylene. Their formation from and their ready conversion into glycol (replacement of Cl or Br by OH) support the structure given above, as glycol with HCl readily gives glycol chlorhydrin  $\text{C}_2\text{H}_4\text{Cl}(\text{OH})$  and this oxidized gives chloracetic acid (Chap. VI, D.) in which it can be proved that the Cl and OH are attached to different carbon atoms and hence in the chlorhydrin the Cl and OH, in glycol the two OH groups, and in ethylene dibromide the two Br atoms are attached to different carbon atoms.

The **Ethylidene compounds** are obtained from aldehyde (para-aldehyde) by exchange of the oxygen for halogen by means of phosphorus chloride, &c. **Ethylidene chloride**, ethidene chloride, or 1 : 1-dichloroethane, is most conveniently prepared with phosgene,  $\text{COCl}_2$ , thus:



It is also formed by the further chlorination of  $\text{C}_2\text{H}_5\text{Cl}$ , and is a by-product in the manufacture of chloral. Its boiling-point

(57°) is lower than that of ethylene chloride (84°). It is an anæsthetic.

**Propylene chlorides**,  $C_3H_6Cl_2$ , bromides and iodides, are likewise known. One group is formed by the addition of halogen to propylene, and thus has an unsymmetrical constitution, e.g. propylene chloride, 1 : 2-dichloropropane,  $CH_3 \cdot CHCl \cdot CH_2Cl$ . Isomeric with this group are the symmetrically-constituted **Trimethylene derivatives**, of which trimethylene-bromide, 1 : 3-dibromo-propane,  $CH_2Br \cdot CH_2 \cdot CH_2Br$ , results from the addition of hydrobromic acid to allyl bromide:



### TRI-SUBSTITUTION PRODUCTS

**Chloroform**,  $CHCl_3$  (*Liebig* and *Soubeiran*, 1831; formula established by *Dumas*, 1835).

*Formation*.—Of theoretical interest is its formation from methane or methyl chloride. A common method of preparation is by the action of bleaching powder on alcohol or acetone. An improved method is the saturation of alcohol with chlorine and treatment of the product with lime and a little bleaching powder. To obtain pure chloroform on a small scale, chloral or its hydrate is warmed with alkali solution,  $CCl_3 \cdot CHO + NaOH \rightarrow CHCl_3 + H \cdot COONa$ . It is highly probable that aldehyde and chloral are intermediate products when alcohol is used. It can also be obtained electrolytically from alcohol or acetone and alkali or alkali-earth chloride solutions (*Z. Elec.*, 1919, **25**, 115).

It is a colourless liquid of a peculiar ethereal odour and sweetish taste, is sparingly soluble in water, and solidifies below  $-70^\circ$ . B.-pt.  $61.2^\circ$ . Sp. gr. 1.527. It dissolves fats, resins, caoutchouc, iodine, &c., and is also a most valuable anæsthetic (*Simpson*, Edinburgh, 1848).

The carbylamine reaction (see Iso-nitriles) furnishes a delicate test for the presence of chloroform.

**Bromoform**,  $CHBr_3$ , is sometimes present in commercial bromine.

**Iodoform**,  $CHI_3$  (*Serullas*, 1822; formula established by *Dumas*), is prepared by warming alcohol with iodine and alkali or alkali carbonate:



It can also be prepared in the same way from acetone, aldehyde, lactic acid, and, generally, from compounds which contain the group  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{C}$ , or  $\text{CH}_3\cdot\text{CO}\cdot\text{C}$  (*Lieben*).

An electrolytic method consists in passing a current through a solution containing potassium iodide, sodium carbonate, and alcohol, the temperature being kept at  $65^\circ$ . Some 85 per cent of the potassium iodide is thus converted into iodoform.

It crystallizes in yellow hexagonal plates, melts at  $119^\circ$ , has a peculiar odour, is volatile with steam, and is an important antiseptic. It contains only 0.25 per cent H, which at first caused the presence of the latter to be overlooked.

The compound  $\text{CHCl}_2\text{F}$ , obtained from  $\text{CHCl}_3$  and  $\text{SbF}_3$ , has b.-pt.  $-20^\circ$ , and is used in refrigerating and air-conditioning plants.

**Methyl chloroform**,  $\text{CH}_3\cdot\text{CCl}_3$ . This compound, the trichloride of acetic acid, also acts as an anæsthetic.

**Glyceryl chloride**, *Trichlorhydrin*, 1 : 2 : 3-trichloropropane,  $\text{CH}_2\text{Cl}\cdot\text{CHCl}\cdot\text{CH}_2\text{Cl}$ , is obtained from glycerol and  $\text{PCl}_5$  (p. 64). B.-pt.  $158^\circ$ . The corresponding bromine compound is also known, but not the iodine one,  $\text{C}_3\text{H}_5\text{I}_3$ , as it immediately decomposes (i.e. when glycerine, phosphorus, and iodine react together) into allyl iodide,  $\text{C}_3\text{H}_5\text{I}$ , and  $\text{I}_2$ .

## HIGHER SUBSTITUTION PRODUCTS

**Carbon tetrachloride**,  $\text{CCl}_4$ , prepared from chloroform or carbon disulphide and chlorine, is a colourless liquid, and is used as a solvent for fats, and in fire extinguishers.

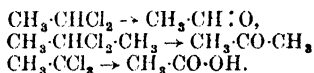
The tetrabromide, from bromine and  $\text{CS}_2$ , is sometimes used for brominating, e.g. alkylbenzenes (*J. A. C. S.*, 1932, 2025).

**Perchloro-ethane**,  $\text{C}_2\text{Cl}_6$ . Rhombic plates of camphor-like odour. Melts and sublimes at  $185^\circ$ . For other halogen derivatives of ethane, cf. Chap. LI, F.

The chemical properties of these polyhalogen derivatives are somewhat similar to those of the monohalogen derivatives. They may be reduced, transformed into the corresponding alcohols, or the halogen atoms replaced by  $\text{NH}_2$  radicals, &c. The action of alkalis on the polyhalogen derivatives, in which the halogen atoms are attached to the same carbon atom, is interesting. They do not yield di- or tri-hydroxy compounds as such compounds with two or more OH groups attached to



the same carbon atom are unstable and lose water, yielding aldehydes, ketones or acids:

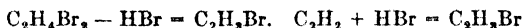


As a rule moderately high temperatures are required.

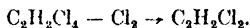
## B. Halide Derivatives of the Unsaturated Hydrocarbons

### (a) From Olefines.

These compounds are obtained either by eliminating part of the halogen as halogen hydride from the di-halogen derivatives of the saturated hydrocarbons, or by incompletely saturating the hydrocarbons poorer in hydrogen with halogen or halogen hydride, e.g.:



or by elimination of  $\text{Cl}_2$  from the saturated tetrahalogen derivatives by the action of zinc dust:



These unsaturated products are very similar to the corresponding saturated ones, but they are, of course, capable of combining further with halogen or halogen hydride, and they exist in stereo-isomeric modifications. (See Fumaric Acid.)

When the halogen atom is attached to one of the C atoms forming the olefine link, as in the vinyl compounds, it is not so readily replaceable by OH,  $\text{NH}_2$ , CN as in the saturated halides.

**Vinyl chloride**, chloroprene, chloroethene,  $\text{CH}_2:\text{CHCl}$ , is of commercial value for the manufacture of duprene (cf. Artificial rubbers, Chap. LXI, E.), and is formed from acetylene and HCl.

**Vinyl bromide** is usually prepared from ethylene di-bromide and alkali.

**Allyl-chloride**, -bromide, and -iodide, 3-iodo-1-propene,  $\text{CH}_2:\text{CH}\cdot\text{CH}_2\text{X}$ , are of importance on account of their relation to the allyl compounds found in nature, e.g. oil of mustard and oil of garlic. They are usually prepared from the alcohol,

allyl alcohol, but the iodide is prepared from glycerol, phosphorus, and iodine, and from it, by means of  $\text{HgCl}_2$ , the chloride. In these compounds the halogen is more reactive than in the common alkyl halides.

Isomeric with these are the **propylene compounds**, e.g.  **$\alpha$ -chloro-propylene** (1-chloro-1-propene),  $\text{CHCl}:\text{CH}\cdot\text{CH}_3$ .

**Trichloroethylene** (*Westrosol*),  $\text{CCl}_2:\text{CHCl}$ , a heavy liquid boiling at  $88^\circ$ , is an important solvent for fats, and is formed by the action of dilute alkalis on **acetylene tetrachloride**,  $\text{CHCl}_2\cdot\text{CHCl}_2$ , a product formed by the union of acetylene and chlorine (Chap. LI, F.).

From acetylene are formed the *Grignard* reagents,  $\text{CH}:\text{CMgBr}$  and  $\text{BrMg}\cdot\text{C}:\text{C}\cdot\text{MgBr}$ , which are used for synthesizing unsaturated alcohols and glycols (Abs., 1914, i, 393, 401, 405).

### III. MONOHYDRIC ALCOHOLS, OR ALKYL HYDROXIDES

Alcohols may be regarded as paraffins in the molecules of which one or more hydrogen atoms have been replaced by one or more univalent *hydroxyl* groups,  $\cdot\text{O}\cdot\text{H}$ . The  $\cdot\text{O}\cdot\text{H}$  group is thus characteristic of alcohols. For the proof of the presence of the OH group, see p. 10. They are usually divided into groups, according to the number of such radicals contained in the molecule: *dihydric*, e.g.  $\text{C}_2\text{H}_4(\text{OH})_2$ ; *trihydric*, e.g.  $\text{C}_3\text{H}_5(\text{OH})_3$ ; *hexahydric*, e.g.  $\text{C}_6\text{H}_8(\text{OH})_6$ , &c.

The monohydric alcohols are either saturated or unsaturated, according to the hydrocarbons from which they are derived. The unsaturated closely resemble the saturated, except that they are capable of forming additive compounds.

#### A. Monohydric Saturated Alcohols, $\text{C}_n\text{H}_{2n+1}\text{OH}$

(See Table, p. 73)

The lowest members of this series are colourless mobile liquids, the middle ones are more oily, and the highest—from dodecyl alcohol,  $\text{C}_{12}\text{H}_{25}\text{OH}$ , onwards—are solid at the ordinary temperatures, and like paraffin in appearance. Gaseous

alcohols are unknown; and it is thus obvious that the introduction of OH for H raises the boiling-point of a substance. Compare:

	B.p.		B.p.
CH <sub>4</sub> .. ..	-161.4° ..	CH <sub>3</sub> OH .. ..	64.5°
C <sub>2</sub> H <sub>6</sub> .. ..	-88.3° ..	C <sub>2</sub> H <sub>5</sub> OH .. ..	78.5°
C <sub>2</sub> H <sub>5</sub> (OH) ..	78.5° ..	C <sub>2</sub> H <sub>4</sub> (OH) <sub>2</sub> ..	197.5°

With compounds of analogous constitution the boiling-point rises with tolerable regularity; in the case of the lower members by about 19°, and higher up in the series by a smaller number.

The lowest members are miscible with water, but this solubility rapidly diminishes as the molecular weight increases; thus butyl alcohol requires 12 parts, and amyl alcohol 40 parts of water for solution, while the higher members are no longer soluble in water. The former can be separated or "salted out" from their aqueous solution by the addition of salts, e.g. K<sub>2</sub>CO<sub>3</sub> and CaCl<sub>2</sub>.

The specific gravity is always < 1. The highest members (over C<sub>16</sub>) can be distilled undecomposed only in a vacuum; at the ordinary pressure they break up into olefine and water. The lowest members possess a spirituous odour, those with more than five C atoms an odour of fusel, and both have a burning taste, while the highest members are like paraffin in appearance and without either taste or smell.

#### CONSTITUTION AND ISOMERS; CLASSIFICATION OF THE ALCOHOLS

Propyl alcohol, C<sub>3</sub>H<sub>7</sub>·OH, and the higher members exist in different isomeric modifications; thus there are two propyl, four butyl, and eight amyl alcohols, &c.

The number of isomeric forms theoretically possible can be determined by taking the formulæ for the corresponding saturated hydrocarbons, and seeing in how many different positions the OH group can be introduced, e.g. CH<sub>3</sub>·CH<sub>2</sub>·CH<sub>3</sub>, propane can obviously give:



two distinct propyl alcohols.

# NORMAL MONOHYDRIC SATURATED ALCOHOLS

Name	Syst. Name	Const. Formula	Melting-pt.	Boiling-pt.	Sp. gr. at 0°
Methyl alcohol	Methan-1-ol	CH <sub>3</sub> ·OH	-97.8°	64.5°	0.812
Ethyl alcohol	Ethan-1-ol	CH <sub>3</sub> ·CH <sub>2</sub> ·OH	-117.3	78.5	0.806
n-Propyl alcohol	Propan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>2</sub> ·OH	-127	97.8	0.817
n-Butyl alcohol	Butan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>3</sub> ·OH	-89.8	117.7	0.823
n-Amyl alcohol	Pentan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>4</sub> ·OH	-75.5	137.9	0.829
n-Hexyl alcohol	Hexan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>5</sub> ·OH	-51.6	155.8	0.833
n-Heptyl alcohol	Heptan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>6</sub> ·OH	-34.6	175.8	0.836
n-Octyl alcohol	Octan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>7</sub> ·OH	-16.3	194	0.839
n-Nonyl alcohol	Nonan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>8</sub> ·OH	-5	215	0.842
n-Decyl alcohol	Decan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>9</sub> ·OH	7	231	0.839
n-Dodecyl alcohol	Dodecan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>11</sub> ·OH	24	259	0.831 at 24°

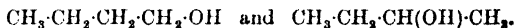
# ISOMERIC PROPYL, BUTYL, AND AMYL ALCOHOLS

Name	Syst. Name	Const. Formula	B.pt.	Sp. gr. at 20°
<i>Propyl alcohols</i> —C <sub>3</sub> H <sub>7</sub> ·OH.				
Normal	Propan-1-ol	CH <sub>3</sub> ·CH <sub>2</sub> ·CH <sub>2</sub> ·OH	97.8°	0.804
Iso or secondary	Propan-2-ol	CH <sub>3</sub> ·CH(OH)·CH <sub>3</sub>	82.3	0.789
<i>Butyl alcohols</i> —C <sub>4</sub> H <sub>9</sub> ·OH.				
Norm. primary	Butan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>3</sub> ·OH	117.7	0.810
Norm. secondary	Butan-2-ol	CH <sub>3</sub> ·CH <sub>2</sub> ·CH(OH)·CH <sub>3</sub>	99.5	..
Prim. isobutyl	2-Methyl-propan-1-ol	(CH <sub>3</sub> ) <sub>2</sub> ·CH·CH <sub>2</sub> ·OH	107.3	0.806
Tertiary	2-Methyl-propan-2-ol	(CH <sub>3</sub> ) <sub>3</sub> ·C·OH	82.8	0.786
<i>Amyl alcohols</i> —C <sub>5</sub> H <sub>11</sub> ·OH				
Norm. primary	Pentan-1-ol	CH <sub>3</sub> ·[CH <sub>2</sub> ] <sub>4</sub> ·OH	138	..
Isobutyl carbinol	2-Methyl-butan-4-ol	(CH <sub>3</sub> ) <sub>2</sub> ·CH·CH <sub>2</sub> ·CH <sub>2</sub> ·OH	131	..
Secondary butyl carbinol	2-Methyl-butan-1-ol	CH <sub>3</sub> ·CH <sub>2</sub> ·CH(CH <sub>3</sub> )·CH <sub>2</sub> ·OH	128	..
Methyl-propyl carbinol	Pentan-2-ol	CH <sub>3</sub> ·CH <sub>2</sub> ·CH <sub>2</sub> ·CH(OH)·CH <sub>3</sub>	119	..
Methyl-isopropyl carbinol	2-Methyl-butan-3-ol	(CH <sub>3</sub> ) <sub>2</sub> ·CH·CH(OH)·CH <sub>3</sub>	112.5	..
Diethyl carbinol	Pentan-3-ol	CH <sub>3</sub> ·CH <sub>2</sub> ·CH(OH)·CH <sub>2</sub> ·CH <sub>3</sub>	117	..
Dimethyl-ethyl carbinol	2-Methyl-butan-2-ol	(CH <sub>3</sub> ) <sub>2</sub> ·C(OH)·CH <sub>2</sub> ·CH <sub>3</sub>	102	..

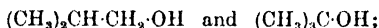
Butane exists in two forms:



From the *n*-butane are derived:



from the *iso*:



but no more.

Of these isomerides, some only are oxidizable to acids,  $\text{C}_n\text{H}_{2n}\text{O}_2$ , containing an equal number of carbon atoms, an aldehyde,  $\text{C}_n\text{H}_{2n}\text{O}$ , being formed as intermediate product. Such alcohols are termed **primary** alcohols (primary propyl, butyl, and isobutyl alcohols, &c.).

Another class of alcohols is not oxidizable to acids with an equal number of atoms of carbon, but to ketones,  $\text{C}_n\text{H}_{2n}\text{O}$ , by the removal of 2 atoms of hydrogen, e.g. isopropyl alcohol yields acetone,  $\text{C}_3\text{H}_6\text{O}$ . These are termed **secondary** (secondary butyl alcohol). Upon further oxidation the ketones do indeed yield acids, which, however, contain not an equal but always a smaller number of carbon atoms, as the result of a rupture of the carbon chain.

Lastly, the third class of alcohols, the **tertiary**, yield upon oxidation neither aldehydes, ketones, nor acids with an *equal* but always a smaller number of carbon atoms, due to the fission of the carbon chain.

**Constitution of Alcohols.**—In the molecule of a monohydric alcohol one of the hydrogen atoms plays a part different from that of the others; thus it is replaceable by metals (K and Na), and by acid radicals, and, together with the oxygen atom, combines with the hydrogen of a halogen hydride to form water, while the other hydrogen atoms of the alcohol remain unchanged. This hydrogen atom, which has already been formulated under the Theory of Types apart from the others, is called the "typical" or "extra-radical" hydrogen atom. It is not joined directly to the carbon atom, but through the oxygen one, a conclusion which is confirmed by the formation of alcohols by the action of alkalis (KOH) on monohalogen derivatives of the paraffins. (See p. 77). This point has been previously discussed (p. 10) for ethyl alcohol.

The alcohols therefore contain a hydroxyl group, OH, and their general constitutional formula is  $(\text{C}_n\text{H}_{2n+1})\cdot\text{OH}$ .

According to theory, this hydroxyl can either replace an atom of hydrogen in a methyl group, in which case an alcohol containing the group  $\cdot\text{CH}_2\text{OH}$  (one carbon atom being joined to the other by a single bond) results, e.g.  $\text{CH}_3\cdot\text{CH}_2\cdot\text{OH}$ . Or it can replace the hydrogen of a  $\text{CH}_2$  group in a hydrocarbon, so that the resulting compound contains the group  $\cdot\text{CH}\cdot\text{OH}$ , the carbon being here joined to two other carbon atoms. Or, lastly, it is possible that in a hydrocarbon with a branching carbon chain, the hydrogen of a methine group  $\text{CH}$  may be replaced by hydroxyl, when the resulting alcohol would contain the group  $\cdot\text{C}\cdot\text{OH}$ , in which one carbon atom is joined to three others.

Now, it is easy to see that the group  $\cdot\text{C}\begin{array}{l} \text{H}_2 \\ \text{O}\cdot\text{H} \end{array}$  can, by further oxidation, be transformed into  $\cdot\text{C}\begin{array}{l} \text{O} \\ \text{O}\cdot\text{H} \end{array}$ . The latter, which is termed carboxyl, is contained in the acids  $\text{C}_n\text{H}_{2n}\text{O}_2$ , or  $\text{C}_{n-1}\text{H}_{2n-1}\text{COOH}$ , which are formed by the oxidation of the primary alcohols. Consequently it is the **primary** alcohols which contain the group  $\cdot\text{CH}_2\cdot\text{OH}$ .

The group  $\cdot\text{CH}\cdot\text{OH}$  can likewise be changed into  $\cdot\text{C}\cdot\text{O}$  (i.e.  $\text{C}\begin{array}{l} \text{OH} \\ \text{OH} \end{array} - \text{H}_2\text{O}$ ), which is the characteristic group of the ketones, by oxidation. A further introduction of O or OH, whereby acids containing the group  $\cdot\text{CO}\cdot\text{OH}$  would ensue, is not possible in this case without a rupture of the carbon chain, since the carbon atom is tetravalent. Since then it is the **secondary** alcohols which upon oxidation yield ketones, and not acids with an equal number of carbon atoms, the group  $\cdot\text{CH}\cdot\text{OH}$  is characteristic of these.

Finally, the group  $\cdot\text{C}\cdot\text{OH}$  already contains the maximum of oxygen which can be combined with a carbon atom already linked to 3 other atoms of carbon. A compound, therefore, in which this atomic group is present, cannot yield, when oxidized, an aldehyde, acid, or ketone with an equal number of carbon atoms in the molecule, but the result of such oxidation must be the breaking of the carbon chain, and the formation of acids or ketones containing a smaller number of carbon atoms in the molecule. This being the behaviour of **tertiary**

alcohols, the group  $\text{:C}\cdot\text{OH}$  is peculiar to them. The existence of the three classes of alcohols finds in this way a thoroughly satisfactory explanation from theory.

Secondary and tertiary alcohols were predicted by *Kolbe* in 1859 from theoretical considerations (A., 113, 301; 132, 102).

Among the isomeric alcohols the primary possess the highest, and the tertiary the lowest boiling-points (cf. p. 73). Similar generalizations appear to hold good for other physical properties; specific gravity, specific refractive indices, and capillarity constants. The tertiary have the highest melting-points.

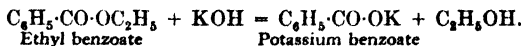
*Determination of Constitution.*—The determination of the constitution of any specific alcohol is based largely on its method of formation and on its products of oxidation. E.g. Isopropyl alcohol may be obtained by the reduction of acetone  $(\text{CH}_3)_2\text{C}\text{:O}$ , and must therefore have the constitutional formula  $(\text{CH}_3)_2\text{CH}\cdot\text{OH}$ , and not  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ . This is confirmed by the fact that on oxidation it yields the ketone acetone.

Similarly isobutyl alcohol must be represented as  $(\text{CH}_3)_2\text{CH}\cdot\text{CH}_2\cdot\text{OH}$ , since on oxidation it yields *iso*-butyric acid, the constitution of which is known to be  $(\text{CH}_3)_2\text{CH}\cdot\text{CO}\cdot\text{OH}$ .

A method of distinguishing primary, secondary, and tertiary alcohols is given on p. 107. Another method suggested is the action of dry potassium hydroxide at  $230^\circ$ . Primary alcohols give acids containing the same number of carbon atoms, secondary yield complex alcohols by condensation, and tertiary are unaffected (*Guerbet*, C.R., 1912, 154, 222, 713, 1487).

*Occurrence.*—Different alcohols are found in nature free or combined with organic acids as esters in ethereal oils and waxes.

*I. General Methods of Formation.*—1. By “**saponification**” or “**hydrolysis**” of their esters, i.e. by boiling these with alkalis or mineral acids, or by the action of superheated steam, thus:

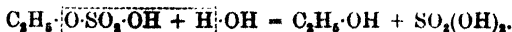


Ethyl benzoate

Potassium benzoate

Most of these processes of hydrolysing require some little time, and the ester is boiled with the alkali KOH solution in a flask fitted with a reflux condenser.

Some esters, e.g. ethyl hydrogen sulphate, decompose when simply warmed with water:



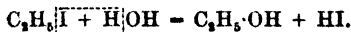
This method is employed on a large scale for the production of many alcohols. The raw materials are the olefines present in natural and cracked gases which are absorbed by sulphuric acid of suitable concentration and the resulting alkyl hydrogen sulphates hydrolysed by boiling with water (cf. p. 76). A separation of a mixture of olefines can be effected by using acid of different concentrations combined with control of temperature. Thus at 30° a 66 per cent acid absorbs *iso*-butylene almost exclusively, 85 per cent acid absorbs *n*- and pseudo-butylenes, 94 per cent acid absorbs propylene, and at 100° 98 per cent acid absorbs ethylene. By using packed towers down which acids of different concentrations pass and gases in the counter direction, nearly theoretical yields can be obtained. The alcohols made by this method are ethyl, *iso*-propyl, *iso*-butyl, secondary butyl, tertiary butyl and most of the amyl alcohols. It is to be noted that no appreciable amounts of primary alcohol—with the exception of ethyl—are formed by this method.

An alternative method is to absorb the olefines in liquid paraffins under pressure and to treat the solutions at suitable temperature and appropriate concentration of sulphuric acid.

By passing olefines into an aqueous solution of zinc sulphate at 200° under pressure good yields of *iso*-propyl or *sec*-butyl alcohols can be obtained.

2. From the halogen compounds  $C_nH_{2n+1}X$ , and therefore indirectly from the paraffins and olefines (pp. 60 and 62). In the latter case secondary or tertiary alcohols, from  $C_3$  on, are obtained since the halogen of the haloid compounds becomes attached to that carbon atom to which the smaller number of hydrogen atoms are united.

(a) By warming these, especially the iodides, with excess of water to 100°; in the case of tertiary iodides by simply allowing the mixture to stand:



It is possible to estimate a tertiary iodide in the presence of a primary or secondary by estimating the amount of HI eliminated by warming with water (A., 1911, 379, 287).

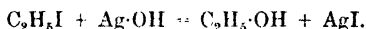
Alkalis can act by replacing halogen by OH or by eliminating HX and thus forming olefines, and in many cases both reactions occur simultaneously. Mild alkalis favour the formation



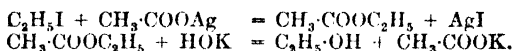
of alcohols and strong concentrated alkalis, particularly alcoholic potash, favour the formation of olefines. In some cases, however, the halogen can become replaced by OEt when concentrated alcoholic potash is used thus yielding an ether as a by-product.

When but little water is used, a state of equilibrium is reached as the reaction is reversible. These halogen compounds may also be termed the esters of the halogen hydracids, so that, strictly speaking, the mode of formation 2a is included in 1.

(b) Frequently by digesting with moist silver oxide (which acts here like the unknown hydroxide, AgOH), or by boiling with lead oxide and water:

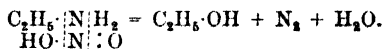


(c) Upon warming with silver or potassium acetate, the acetate of the alcohol in question is formed, and this is then hydrolysed:

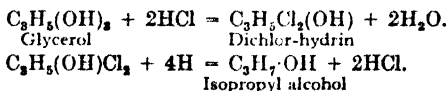


3. By the fermentation of the carbohydrates (e.g. grape-sugar), the alcohols with 2, 3, 4, 5, and, under certain conditions, even 6 atoms of carbon are produced. (Yeast fermentation.)

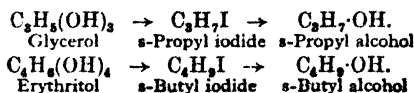
4. On treating the primary amines (see these) with nitrous acid:



5. From polyhydric alcohols by replacing several of the hydroxyl groups by halogen atoms, and then reducing the halogen derivative:



Secondary alkyl iodides are often obtained by the action of HI and P on polyhydric alcohols, and these on hydrolysis yield secondary alcohols, e.g.:

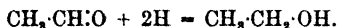


6. Higher alcohols are formed when a lower alcohol is heated with sodium (3 or 4 gm. per gm. mol. of alcohol) and a little copper bronze at 200–260° under pressure (C. I., 1937, 587). From *n*-butyl alcohol the chief product is 2-ethylhexanol,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHEt}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , but esters, e.g. butyl butyrate and 2-ethylhexyl butyrate, are also formed. By using a mixture of propyl and benzyl alcohols the chief product is 2-benzylpropyl alcohol,  $\text{CH}_3\cdot\text{CH}(\text{CH}_2\cdot\text{C}_6\text{H}_5)\cdot\text{CH}_2\cdot\text{OH}$ .

7. Alcohols are formed when esters of higher fatty acids are catalytically hydrogenated under pressure in presence of a nickel-chromium oxide catalyst.

8. Alcohols are formed when esters are reduced with sodium and alcohol (ethyl or amyl) and the method is recommended for preparing the alcohols corresponding with the higher saturated and unsaturated fatty acids (*Bouveault* and *Blanc*, Bull. Soc., 1904, (iii), **31**, 669) (Chap. XLVII, A.).

II. *Special Methods of Formation*.—1. **Primary alcohols** are obtained from aldehydes by reduction with sodium amalgam and very dilute sulphuric acid (*Wurtz*); or with acetic acid and zinc dust, when the alkyl acetates are formed:



This reaction is somewhat similar to the reduction of an olefine to a paraffin. In both cases a double bond is converted into a single bond, and an atom of hydrogen is added on to each atom between which the double bond originally existed.

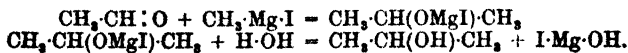
Similarly from acid anhydrides (or esters, but not the free acids) and nascent hydrogen, or by the reduction of the acid chlorides, when an ester of the alcohol is formed by the action of the unreduced chloride on the alcohol.

2. **Secondary alcohols** are formed by the action of nascent hydrogen (sodium amalgam) on the ketones,  $\text{C}_n\text{H}_{2n}\text{O}$ :

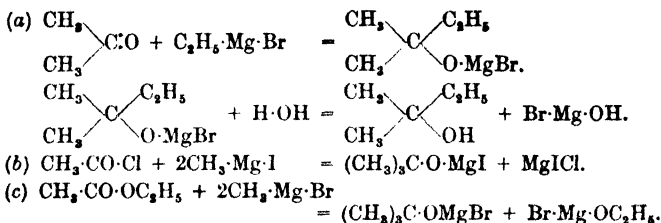


Pinacones are obtained here as by-products. (See Ketones.)

3. **Secondary alcohols** are also formed by the the action of aldehydes on dry ethereal solutions of magnesium alkyl halides (Chap. IV, H.), and treating the product which results with water or dilute acid:



4. **Tertiary alcohols** are formed by the action of (a) ketones, (b) acid chlorides, or (c) **esters of organic acids**, on magnesium alkyl halides (*Grignard reagents*, Chap. IV, H., Ann. Chim., 1901, 24, 433), and decomposing the products with water:



In (b) and (c) addition of  $\text{CH}_3$  and  $\text{MgBr(I)}$  to the  $\text{C:O}$  group occurs just as in (a), but at the same time a  $\text{Cl}$  atom in (b) and an  $\text{OEt}$  group in (c) become replaced by  $\text{CH}_3$ . These methods are a great improvement on the older method of acting on acid chlorides with zinc alkyls (*Butleroff*).

5. **Secondary or tertiary alcohols** sometimes ensue by the direct combination of an olefine with water, e.g. tertiary butyl alcohol,  $(\text{CH}_3)_3\text{C}\cdot\text{OH}$ , from isobutylene. This often gives a simple method for converting a primary into a secondary or tertiary alcohol.

The *Nomenclature* of the alcohols, especially of the secondary and tertiary, is based upon a comparison of them with methyl alcohol, also called carbinol. They are looked upon as carbinol,  $\text{CH}_3\cdot\text{OH}$ , in which the three hydrogen atoms are wholly or partially replaced by alkyl radicals, thus:

Tertiary butyl alcohol,  $(\text{CH}_3)_3\text{C}\cdot\text{OH}$  = trimethyl-carbinol;

Secondary butyl alcohol,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}_3$ ,  
 $= \text{CH}(\text{OH})(\text{CH}_3)(\text{C}_2\text{H}_5)$ , = methyl-ethyl-carbinol.

The systematic name (Geneva nomenclature) of the alcohols terminates in "ol". As examples:

$\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$  Butanol.

$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{CH} \\ \diagup \\ \text{CH}_3 \end{array} \cdot \text{CH}(\text{CH}_3) \cdot \text{CH}(\text{OH}) \cdot \text{CH}_3$  2:3-Dimethylpentan-4-ol.

**Chemical Characteristics.**—The alcohols are much more reactive than the paraffins and this reactivity is due to the presence of the  $\text{OH}$  group. The reactivity varies with the

structure of the molecule, but all have certain properties in common.

1. In many reactions they resemble water; thus an atom of H is readily replaced by metals, e.g. readily by K or Na, less readily by Ca, Mg, or Al with formation of alcoholates,  $\text{EtONa}$ ,  $\text{Mg(OEt)}_2$ , &c. They are not so reactive as water and the  $\text{H}^+$  concentration of pure methyl alcohol is lower than that of water. The Na and Al compounds are of great value for synthetic purposes.



These react with water, giving rise to a state of equilibrium as represented in the equation



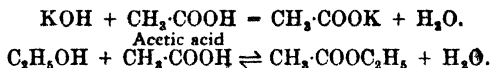
Brühl (B., 1904, 2066, cf. Org. Synths., 1929, 38) has described a method for preparing the compound  $\text{CH}_3\cdot\text{ONa}$  free from water and alcohol.

For general discussion on these metallic compounds, cf. Chem. Rev., 1934, 385. The primary alcohols react most readily and the tertiary least readily with a metal.

Primary and secondary, but not tertiary, alcohols combine with baryta and lime to alcoholates at  $130^\circ$ . Crystalline compounds are formed with calcium chloride, so that this salt cannot be used for drying the alcohols; these compounds are decomposed by water.

2. They enter into the composition of many compounds, as "alcohol of crystallization". (See pp. 83 and 88.)

3. As very feebly basic substances they react with acids both mineral and organic in somewhat the same manner as metallic hydroxides do, yielding **alkyl salts** or **esters** and water (cf. Esterification):



The methyl and ethyl esters derived from certain substituted benzoic acids, e.g. 3:5-di-nitrobenzoic acid (Chap. XXVI, A1), are solids with definite melting-points, and are sometimes used in identifying small amounts of these alcohols.

4. Dehydrating agents convert them into olefines.

5. With halogen hydracids or phosphorus halides, they yield monohalide derivatives of the hydrocarbons (p. 63); the tertiary alcohols react extremely readily and the primary least readily with HCl or HBr (Lucas, J. A. C. S., 1930, 802).

6. For the behaviour of primary, secondary, and tertiary alcohols upon oxidation, see p. 75 *et seq.*

Methyl alcohol is oxidized to carbon dioxide as the primary product (formic acid) is itself readily oxidized.

7. The primary, secondary, and tertiary alcohols can also be distinguished from one another by the behaviour of the nitro-compounds, which are formed by the action of silver nitrite on the iodides (cf. p. 107).

8. Halogens do not substitute but oxidize.

9. Many alcohols when heated with excess of soda lime yield the sodium salts of the corresponding acids.

**Methyl alcohol**, Methanol, Wood Spirit,  $\text{CH}_3\text{OH}$ , was discovered in wood-tar by *Boyle* in 1661, and its difference from ordinary alcohol recognized in 1812 by *Phillips Taylor*. Its composition was established in 1834 by *Dumas* and *Péligot*. It occurs as methyl salicylate in *Gaultheria procumbens* (oil of winter green, Canada), as butyric ester in the unripe seeds of *Heracleum giganteum*, and as ester of benzoylecgonine in cocaine.

*Formation*.—1. By chlorinating methane,  $\text{CH}_4$ , and hydrolysing the resulting methyl chloride (*Berthelot*).

2. By passing  $\text{CO} + \text{H}_2$  over a suitable catalyst, a by-product is a mixture containing higher alcohols (Chap. XLIX, B.).

3. By the destructive distillation of wood (beech, birch, or oak wood) at about  $350^\circ$ . By this distillation there are obtained (a) Gases ( $\text{CH}_4$ ,  $\text{C}_2\text{H}_6$ ,  $\text{C}_2\text{H}_4$ ,  $\text{C}_2\text{H}_2$ ,  $\text{C}_3\text{H}_6$ ,  $\text{C}_4\text{H}_8$ ,  $\text{CO}$ ,  $\text{CO}_2$ ,  $\text{H}_2$ ). (b) An aqueous distillate of "pyroligneous acid", containing methyl alcohol (1–2 per cent), acetic acid (10 per cent), acetone (0.1–0.5 per cent), methyl acetate, allyl alcohol, &c. (c) Wood-tar, containing paraffins, naphthalene, phenol, guaiacols, &c. (d) Wood charcoal.

4. Also by the dry distillation of vinasse.

It is prepared commercially from crude pyroligneous acid by repeated distillation after neutralization with lime, and is purified by formation of the  $\text{CaCl}_2$  compound, which is a solid, and stable at  $100^\circ$ ; or, better, by transformation into the oxalic or benzoic ester, both of which are easy to purify and hydrolyse. At the present time it is largely manufactured by process 2.

*Properties.*—It is a colourless liquid, boils at  $64.5^{\circ}$ , and has a specific gravity about 0.8. The alcohol of commerce usually contains acetone. It burns with a non-luminous flame, dissolves, fats, oils, &c., and acts as an intoxicant like ethyl alcohol. It also enters into the composition of compounds as "alcohol of crystallization", e.g.  $\text{BaO} + 2\text{CH}_3\text{O}$ ;  $\text{MgCl}_2 + 6\text{CH}_3\text{O}$ ;  $\text{CaCl}_2 + 4\text{CH}_3\text{O}$  (six-sided plates). It is readily oxidized to formic aldehyde and formic acid, being also converted into the latter when heated with soda-lime. Potassium methoxide,  $\text{CH}_3\text{OK}$ , is a white crystalline powder, and forms a definite crystalline compound  $\text{CH}_3\text{OK} + \text{CH}_3\text{OH}$ .

The anhydrous alcohol dissolves a small amount of dehydrated cupric sulphate to a blue-green solution. Distilled over heated zinc dust, it decomposes almost quantitatively into  $\text{CO} + 2\text{H}_2$ .

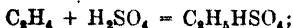
*Uses.*—For tar colours—(also as  $\text{CH}_3\text{I}$  and  $\text{CH}_3\text{Cl}$ ); as methyl ether in the manufacture of ice; for polishes and varnishes; as *Wiggersheim's* preservative liquid; for methylating or "denaturing" spirits of wine, and as a petrol substitute.

**Ethyl alcohol**, Ethanol, *Spirits of Wine*,  $\text{C}_2\text{H}_5\text{OH}$ . Liquids containing spirits of wine have been known from very early times, and their concentration either by distillation or by dehydration with carbonate of potash is also an old art. We read of it as "alcohol" in the sixteenth century. *Lavoisier* arrived at the qualitative, and *de Saussure* in 1808 the quantitative composition of alcohol. (Cf. E. F. Armstrong, *Alcohol through the ages*, C. I., 1933, 251, 279.)

In the vegetable kingdom alcohol is only found occasionally, as ethyl butyrate, but in the animal kingdom it occurs in various forms, e.g. in diabetic urine. It is also present in small quantity in coal-tar, bone oil, wood spirit, and bread, fresh English bread containing 0.3 per cent.

*Formation.*—1. From  $\text{C}_2\text{H}_6$  by conversion into  $\text{C}_2\text{H}_5\text{Cl}$  and hydrolysis of the latter; cf. methods of formation 1 and 2.

2. Ethylene and concentrated  $\text{H}_2\text{SO}_4$  react at  $160^{\circ}$ , yielding ethyl hydrogen sulphate (*Faraday*, *Hennell*, 1826, *Berthelot*, 1855).



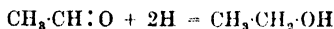
and this when boiled with water gives ethyl alcohol (cf. p. 76). This is a method of commercial importance, particularly in

U.S.A., where the ethylene in natural and cracked gases is utilized.

Ethylene and water can be made to unite, yielding ethyl alcohol by passing them in the vapour phase over thoria or phosphoric acid at 500° and 25–200 atm. pressure or over calcium phosphate at 100–300° and 70 atmospheres. The percentage conversion is small.

3. By absorption of acetylene in 95 per cent sulphuric acid in the presence of cuprous sulphate or petroleum to facilitate absorption; dilution to 64 per cent sulphuric acid and subsequent fractional distillation.

4. By the reduction of acetaldehyde, e.g. the commercial method of passing aldehyde vapour (from acetylene) and hydrogen over finely divided Ni at 140°.



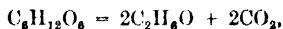
5. *Preparation by the Alcoholic Fermentation of Sugar.*—Directly from grape and fruit sugars,  $\text{C}_6\text{H}_{12}\text{O}_6$ , and indirectly from cane sugar,  $\text{C}_{12}\text{H}_{22}\text{O}_{11}$ , after previous hydrolysis to two molecules of  $\text{C}_6\text{H}_{12}\text{O}_6$ ; also indirectly from malt-sugar, from starch, &c.

*Fermentations* are peculiarly slow decomposition-processes of organic substances which are accompanied, as a rule, with liberation of gas and evolution of heat, and which are induced by micro-organisms or by complex organic nitrogenous substances (*enzymes*) of animal or vegetable origin. The alcoholic fermentation of sugar, i.e. the fermentation which produces spirit, is caused by the varieties of the genus *Saccharomyces*, the *yeast ferment*, which forms small oval microscopic cells, multiplying by gemmation. As plants, these require for their sustenance inorganic salts, e.g. phosphates, potassium salts, and nitrogen in the form of ammonium salts, but, as non-assimilating fungi, no carbon dioxide.

The usual species is *S. cerevisiae*, and several varieties of this are used industrially. It is necessary to keep as pure a culture as possible as other species (wild yeasts) which may be present increase more rapidly than *cerevisiae*. These produce deterioration of the product and affect the yield of alcohol.

All potable alcoholic liquors are made by this method and also very large quantities of power or industrial alcohol used for admixture in motor fuel, particularly in Germany and U.S.A.—in the latter country 23 million gallons in 1936.

In the vinous fermentation 94 to 95 per cent of the grape sugar breaks up into alcohol and carbon dioxide,



with 2.5 to 3.6 per cent glycerol,  $C_3H_5(OH)_3$ , and 0.4 to 0.7 per cent succinic acid,  $C_4H_6O_4$ , as invariable by-products. In addition to these, most of the higher homologues of ethyl alcohol are also formed—the so-called *fusel oil*.

The chief constituent of fusel oil is fermentation amyl alcohol (isobutyl carbinol),  $C_5H_{11}OH$ , but it has also been proved to contain the two propyl alcohols (chiefly isopropyl), normal, iso-, and tertiary butyl alcohols, normal and active amyl alcohols, together with higher homologues and esters. They can be separated by means of their hydrobromic esters.

*Conditions of Fermentation.*—Fermentation can only go on between the limits of 3° and 35°, the most favourable temperature being between 25° and 30°. The solution must not be too concentrated, as the organism cannot live in a solution of alcohol of greater concentration than 14 per cent; the presence of air is not strictly necessary, but it has a favouring influence. Yeast loses its activity upon the addition of any reagents which destroy the cells, also when it is thoroughly dried, when heated to 60°, when treated with alcohol, acids, and alkalis; the addition of small quantities of salicylic acid, phenol, corrosive sublimate, &c., also prevents fermentation.

For a number of years it was thought that the presence of the living yeast plant, or of some other similar organism, was essential for the production of alcoholic fermentation. The work of *E. Buchner* (B., 1897, 2086, 2372; 1898, 971, 2764) has shown that the fermentation is brought about by an enzyme called *zymase*, which is contained in the cell. If the yeast cells are crushed with "Kieselguhr" (a siliceous earth) and water, so that the cell walls are broken, and the mass then filtered through a Chamberland filter under considerable pressure, an extract is obtained which, although practically free from yeast cells, can yet induce alcoholic fermentation. The *zymase* is relatively unstable and easily decomposed, e.g. when the solution is heated or even kept for some time, but it may be preserved by the addition of certain antiseptic substances, such as chloroform, thymol, &c., which readily kill the yeast plant itself. (Compare Chap. LXIX, A.)

Buchner's researches indicate that fermentations induced by



organized ferments are probably due to certain unorganized ferments (enzymes) contained in the cells of the organism.

The following materials are used for the preparation of alcohol or of liquids containing alcohol:

(a) Grape-sugar, fruit-sugar, i.e. grapes and other ripe fruits, for wine, &c. (b) Cane or beet sugar and molasses for brandy. Solutions of cane-sugar are fermented by yeast, since ordinary yeast always contains small amounts of an enzyme (*invertase*), which can hydrolyse cane-sugar to glucose and fructose, and these are then directly fermented by the yeast organism. (c) The starch of cereals for beer and corn brandy, and of potatoes for potato brandy. The starch is first converted into malt-sugar and dextrine under the influence of diastase, or into grape-sugar, by boiling with dilute acids, and these sugars are then fermented. (d) Wood or straw, i.e. cellulose (Chap. XIV, C.), by acid hydrolysis in the presence of a catalyst and subsequent fermentation of the glucose so formed. (e) The waste liquors of the sulphite process for producing pulp from wood; the product contains methyl alcohol; 15 million litres were produced by this method in Sweden in 1930.

The transformation of starch into malt-sugar (maltose) and dextrine is a typical example of fermentation by an *enzyme*, the special enzyme in this case being *diastase* (malt amylase), a complex organic nitrogen derivative produced during the germination of the barley in the process of malting. The transformation of the starch into maltose, &c., is in reality a process of hydrolysis induced by the ferment. The maltose  $C_{12}H_{22}O_{11}$  in its turn is hydrolysed by a second ferment (*maltase*) to grape-sugar,  $C_6H_{12}O_6$ , which is then transformed into alcohol and carbon dioxide.

A wine of medium strength contains  $8\frac{1}{2}$  to 10 per cent alcohol, port wine 15 per cent, sherry up to 21 per cent, champagne 8 to 9 per cent, and beer an average of 3 to 5 for lager or mild and 5 to 9 for old ale.

The different varieties of brandy or spirits obtained by "burning", i.e. by distilling fermented liquids, contain 30 to 40 per cent of alcohol, and cognac even over 50 per cent.

*Purification of alcohol.*—It is impossible to separate alcohol completely from water by distillation, as a mixture containing 95.6 per cent by weight of alcohol has a boiling-point  $78.15^\circ$  which is below that of pure alcohol. When aqueous alcohol is fractionally distilled this azeotropic mixture passes over first

and the residue consists of the excess water. This product, rectified spirits of wine, is the one obtained by using dephlegmators or fractionating columns.

On the laboratory scale aqueous alcohol can be deprived of the greater part of its water by the addition of strongly heated carbonate of potash or anhydrous copper sulphate, or by distillation over quicklime, and the last portions can be removed by several additions of small amounts of metallic calcium and repeated distillation. Alcohol containing water becomes turbid on being mixed with benzene, carbon bisulphide, or liquid paraffin oil, and it gives a white precipitate of  $\text{Ba}(\text{OH})_2$  on the addition of a solution of  $\text{BaO}$  in absolute alcohol, and is capable of restoring the blue colour to anhydrous copper sulphate. Alcohol free from water is termed *absolute* alcohol. Ordinary absolute alcohol usually contains at least 0.2 per cent of water.

Absolute alcohol is now usually manufactured by adding a third liquid to the 95.6 per cent alcohol. The common ones used are benzene and tri-chlorethylene, but toluene, hexane, carbon tetrachloride or methylene dichloride can be employed (C. I., 1942, 120). Each of these compounds forms a low-boiling ternary azeotrope with water and alcohol. When the mixture is distilled the ternary azeotrope passes over first, thus removing all the water, a binary azeotrope of benzene and alcohol follows and finally practically pure absolute alcohol.

Contraction takes place on mixing alcohol and water together, 53.9 volumes alcohol + 49.8 volumes water giving not 103.7, but 100 volumes of the mixture. The percentage of alcohol in any spirit is determined either from its specific gravity by reference to a specially-calculated table, or by areometers of particular construction, or by its vapour tension as estimated by *Geissler's* vaporimeter.

*Properties.*—It is a colourless mobile liquid with characteristic spirituous odour; boils at  $78.5^\circ$ , or at  $13^\circ$  under 21 mm. mercury pressure. Solidifies at  $-117.3^\circ$ , and has sp. gr. 0.79 at  $15^\circ$ . It burns with an almost non-luminous flame, is exceedingly hygroscopic, and miscible with water and with ether in all proportions. Forms several cryo-hydrates with water (+12 Aq., +3 Aq., + $\frac{1}{3}$  Aq.). Is an excellent solvent for many organic substances such as resins and oils, and also dissolves sulphur, phosphorus, &c., to some extent. It is extensively used in industry. As a solvent it is used in the perfumery industry, and also for dissolving resins and oils. It

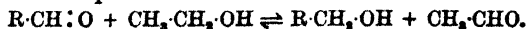
is also used either alone or mixed with benzene or petrol as a fuel in internal-combustion engines, and it is the raw material from which such chemicals as ether, aldehyde, chloroform, iodoform, ethyl chloride and other ethyl esters, vinegar and butyl alcohol are manufactured. It coagulates albumen, being therefore used for preserving anatomical preparations.

It is very readily oxidized by the oxygen of the air, either in presence of finely-divided platinum or in dilute solutions in presence of certain ferments, first to aldehyde and then to acetic acid; thus, beer and wine become sour, but not the pure alcohol itself.  $K_2Cr_2O_7$  or  $MnO_2 + H_2SO_4$  oxidize it in the first instance to aldehyde; fuming nitric acid attacks it with explosive violence, yielding numerous products; but, by the action of colourless concentrated  $HNO_3$ , ethyl nitrate can be obtained under suitable conditions; in dilute solution glycollic acid is formed. Alkalis also induce a gradual oxidation in the air; thus, alcoholic potash or soda solutions quickly become brown with formation of aldehyde resin, this latter resulting from the action of the alkali upon the aldehyde first produced. Alcoholic potash therefore frequently acts as a reducing agent, e.g. upon aromatic nitro-compounds. (See these.) Chlorine and bromine first oxidize alcohol to aldehyde and then act as substituents. (See Chloral.) Chlorinated alcohols can therefore only be prepared indirectly (cf. Ethylene chlorhydrin.) When the vapour of alcohol is led through a red-hot tube,  $H$ ,  $CH_4$ ,  $C_2H_4$ ,  $C_2H_2$ ,  $C_2H_6$ ,  $C_{10}H_8$ ,  $CO$ ,  $C_2H_4O$ ,  $C_2H_4O_2$ , &c., are formed.

Of the compounds containing alcohol of crystallization may be mentioned,  $KOH + 2C_2H_5O$ ,  $LiCl + 4C_2H_5O$ ,  $CaCl_2 + 4C_2H_5O$ , and  $MgCl_2 + 6C_2H_5O$ .

**Sodium ethoxide**,  $C_2H_5ONa$ , is of special importance among the alcoholates. It is formed by the action of sodium upon absolute alcohol. The crystals of  $C_2H_5ONa + 2C_2H_5O$ , at first obtained, lose their alcohol of crystallization at  $200^\circ$  and change into a white powder of  $C_2H_5ONa$ . (See also *Brühl.*) Sodium ethoxide is of especial value for syntheses, and can frequently be employed in alcoholic solution.

The magnesium and aluminium ethoxides  $Mg(OEt)_2$  and  $Al(OEt)_3$  are of value as synthetical reagents; the latter is used for reducing aldehydes and ketones to primary and secondary alcohols in the presence of alcohol:



Unlike most of the other ethoxides the aluminium compound is soluble in benzene and is volatile under reduced pressure. It is regarded as the ester of aluminic acid  $\text{Al}(\text{OH})_3$ , (J. C. S., 1930, 1461).

Small doses of alcohol act as a stimulant, and larger doses as an intoxicant. Absolute alcohol is poisonous, and quickly causes death when injected into the veins. The presence of considerable amounts of fusel oil has detrimental physiological effects.

*Detection of Alcohol.*—1. By the iodoform reaction\* (see Iodoform), when 1 part in 2000 of water can be recognized.

2. By the formation of esters with acid chlorides. With benzoyl chloride it gives ethyl benzoate with its characteristic odour; with *p*-nitro benzoyl chloride, the ethyl ester m.-pt. 57°; and with 3 : 5-dinitrobenzoyl chloride an ethyl ester m.-pt. 93°.

#### Propyl alcohols, $\text{C}_3\text{H}_7\text{OH}$ .

1. **Normal propyl alcohol**, 1-Propanol,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$  (*Chancel*, 1853), is obtained from fusel oil by means of its hydrobromic ester (*Fittig*), or by reduction of the corresponding aldehyde. It has a spirituous odour and is miscible with water in all proportions. Its constitution is based on its relationship to propaldehyde and propionic acid.

The isomer *Secondary* or *iso*-propyl alcohol is a compound of commercial value, and is used as a solvent and as perfume. It is manufactured by the reduction of acetone with sodium amalgam and dilute acid or as a by-product in the hydrogenation of CO at 300° under pressure (cf. Hydrogenation, Chap. XLIX, A.), and also from natural propylene and sulphuric acid.

*n*-Butyl alcohol, 1-butanol,  $\text{CH}_3(\text{CH}_2)_2\cdot\text{CH}_2\cdot\text{OH}$ , is the most important of the butyl alcohols. This alcohol (25 per cent), acetone (11 per cent), and hydrogen are made on the large scale by the fermentation of maize mash with a special bacterium, and the alcohol (cf. Chap. LXIX, B.) is also manufactured in a one-stage catalytic conversion of ethyl alcohol at 400–500° with a BaO catalyst. The other main product is ethyl acetate, but acetal, acetone, acetaldehyde and higher alcohols are also formed. By using ethyl alcohol at 375° with a catalyst of Cu + MgO and pressures of 4000 lb. the product is a mixture of the *n*-alcohol and ethyl acetate.

\* Acetaldehyde, acetone, and isopropyl alcohol also give this reaction, but not methyl alcohol.

It is also formed by the reduction of crotonaldehyde (Chap. V, A.).

*n*-Butyl alcohol and its esters are of great value as solvents in the plastics industry. The secondary alcohol is made from the butylene of cracked gases by absorption in sulphuric acid and hydrolysis.

**Isobutyl-carbinol**,  $(\text{CH}_3)_2\text{:CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , is the chief constituent of the "fermentation amyl alcohol" obtained by fractional distillation of fusel oil, the other constituent being secondary butyl carbinol,  $\text{C}_2\text{H}_5\cdot\text{CH}(\text{CH}_3)\cdot\text{CH}_2\cdot\text{OH}$ .

This latter, on account of its action on polarized light, is generally known as *active* (i.e. optically active) amyl alcohol. It is *laevo*-rotary, i.e. rotates the plane of polarization to the left (cf. active valeric acid, Chap. VI, A.), and has  $[\alpha]_D = 5.9^\circ$  at  $20^\circ$ .

A synthetic amyl alcohol is manufactured from *n*-pentane from light petroleum and natural gas. The first stage is the chlorination in the vapour phase with insufficient chlorine. The crude propyl chloride is digested with an aqueous solution of sodium oleate under pressure and the amyl alcohol so formed distilled over.

The mixture probably contains all the amyl alcohols with the exception of the low-boiling tertiary alcohol.

**Normal hexadecyl alcohol**, or **cetyl alcohol**, forms as palmitic ester the chief constituent of spermaceti. **Ceryl alcohol**, *Cerotin*,  $\text{C}_{26}\text{H}_{53}\text{OH}$ , is present as cerotic ester in Chinese wax. **Melissyl**, or **miricyl alcohol**,  $\text{C}_{30}\text{H}_{61}\text{OH}$ , is present as palmitic ester in bees'-wax and in Carnauba wax (from leaves of Brazilian palm), and is most conveniently prepared from the latter. The alcohols are obtained from all these esters (wax varieties) by hydrolysis with boiling alcoholic potash, and in all probability are mixtures and not pure compounds.

## B. Monohydric Unsaturated Alcohols, $\text{C}_n\text{H}_{2n-1}\text{OH}$

These are very similar to the saturated alcohols both in physical properties and in general chemical behaviour, but are sharply distinguished from the latter by the formation of additive compounds with hydrogen, halogens, halogen hydracids, &c., e.g.:

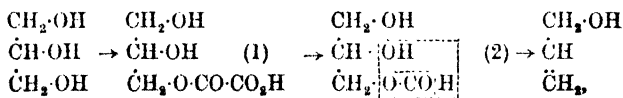


They thus resemble the olefines owing to the presence of a double bond, and the products are saturated alcohols or their halide derivatives, the latter of which cannot be prepared directly by substitution of the alcohols. These unsaturated alcohols are to be considered as olefines in which an atom of hydrogen is replaced by hydroxyl.

Alcohols containing the hydroxy-methylene group,  $:CH(OH)$ , linked to a carbon atom by a double bond, e.g.  $CH_2:CH\cdot OH$ , are not known, although derivatives, e.g. vinyl bromide, are stable. Reactions which might give rise to the unsaturated alcohol **vinyl alcohol** (*ethenol*) yield the more stable isomer,  $CH_3\cdot CHO$  (acetaldehyde); in fact, the grouping  $:C:CH\cdot OH$  is usually unstable, passing as it does into the more stable one,  $:CH\cdot CH:O$ , a transformation which is most readily explained upon the assumption that water is taken up and again split off. Similarly, instead of  $CH_2:C(OH)\cdot CH_3$ , the more stable grouping  $CH_3\cdot CO\cdot CH_3$  is formed.

**Allyl alcohol** (*1-Propene-3-ol*),  $CH_2:CH\cdot CH_2OH$  (*Cahours* and *Hofmann*, 1856), is present to the extent of 0.1 to 0.2 per cent in wood spirit, and is formed (1) from allyl iodide; (2) by reduction of its aldehyde, acrolein (see this); (3) by heating glycerol,  $C_3H_5(OH)_3$ , with oxalic or formic acid and a little ammonium chloride to  $220^\circ$ . (Cf. Formic Acid, p. 173.)

The first product is glyceryl monoxalate (1), which loses  $CO_2$ , forming glyceryl monoformate or monoformin (2).

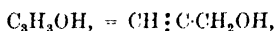


and this when heated to the required temperature,  $220^\circ$ , decomposes into  $CO_2$ ,  $H_2O$ , and allyl alcohol. Allyl alcohol is a mobile liquid with the lachrymatory character of all allyl compounds. It has b.-pt.  $97^\circ$  the same as that of *n*-propyl alcohol and like this is miscible with water. It does not combine directly with hydrogen, but chlorine, bromine, cyanogen, hypochlorous acid, &c. If cautiously oxidized, it yields glycerol, but stronger oxidation converts it into its aldehyde, acrolein, and acid, acrylic acid, containing the same number of carbon atoms, and it is therefore a primary alcohol; hence the above *constitutional formula*.

### C. Monohydric Unsaturated Alcohols, $C_nH_{2n-2}OH$

These alcohols are derivatives of acetylene and its homologues. The compounds possess: (1) The characteristic properties of alcohols. (2) The properties of unsaturated compounds. Each molecule of such an alcohol can combine with 1 or 2 molecules of a halogen or halogen hydracid. (3) Most of them possess the further peculiarity of forming explosive compounds with ammoniacal copper and silver solutions, e.g.  $C_3H_2AgOH$ , the former being coloured yellow and the latter white; acids decompose these compounds into the unsaturated alcohol. Those of them which do not yield such metallic compounds contain, not a triple bond, but two double ones between the carbon atoms. The most important of these alcohols is:

**Propargyl alcohol**, or *propinyl alcohol* (1-Propin-3-ol),



a mobile liquid of agreeable odour, lighter than water, and boiling at  $114^\circ$ , i.e. somewhat higher than normal propyl alcohol.

For further examples of unsaturated alcohols, see Open-chain Terpenes (Chap. LVII, A.).

## IV. DERIVATIVES OF THE ALCOHOLS

These may be classed in the following divisions:

A. Ethers of the alcohols, or alkyl oxides, e.g.  $C_2H_5\cdot O\cdot C_2H_5$ , ethyl ether.

B. Thio-alcohols and ethers, or alkyl hydrosulphides and sulphides, e.g.  $C_2H_5\cdot SH$  and  $(C_2H_5)_2S$ .

C. Esters of alcohols with inorganic acids.

D. Nitrogen bases of the alkyl radicals.

E. Hydroxylamines; Hydrazines.

F. Diazo and Triazo compounds.

G. Alkyl derivatives of phosphorus, arsenic, &c.

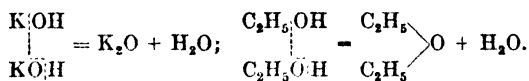
H. Organo-metallic compounds; Grignard compounds.

## A. Ethers Proper (Alkyl- or Alkyl-Oxides)

The ethers of the monohydric alcohols are compounds of neutral character derived from the alcohols by elimination of the elements of water (1 molecule water from 2 molecules alcohol). They can frequently be prepared by treating the alcohols with sulphuric acid, and are distinguished from the latter by not reacting with acids to form esters, and by being substituted and not oxidized by the halogens, &c. Only the lowest member of the series is gaseous, most of them are liquid, and the highest are solid. The more volatile ethers are characterized by a peculiar odour which is not shown by the higher members.

*Constitution.*—The hydrogen atoms cannot be replaced by sodium or other metallic radicals (see p. 10), and are all presumably attached to carbon.

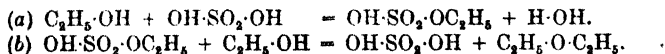
Their structure as alkyl oxides, or anhydrides of monohydric alcohols (cf. metallic oxides), follows largely from modes of formation 2 and 3, from the non-reactive character of the hydrogen atoms, and from reactions 4 and 5, p. 95.



The alkyl groups contained in them may either be the same, as in ordinary ether and in methyl ether,  $(\text{CH}_3)_2\text{O}$ , in which case they are termed “**simple ethers**”; or they may be different, as in methyl-ethyl ether,  $\text{CH}_3\cdot\text{O}\cdot\text{C}_2\text{H}_5$ , when they are known as “**mixed ethers**”.

Ethers derived from tertiary alcohols are not known.

*Modes of Formation.*—1. By heating the alcohols,  $\text{C}_n\text{H}_{2n+1}\cdot\text{OH}$ , with sulphuric acid. The reaction proceeds in two phases, e.g.:



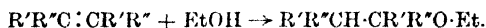
In phase *a* an alkyl hydrogen sulphate is formed, which, when further heated with alcohol, as in *b*, yields ether and regenerates sulphuric acid. The latter is therefore free to work anew, and in this way to convert a very large quantity of alcohol into ether.



This process is theoretically a continuous one, but practically it has its limits, through secondary reactions, such as the formation of  $\text{SO}_2$ , &c. A modification of the method consists in heating the alcohol with benzene-sulphonic acid  $\text{C}_6\text{H}_5\cdot\text{SO}_2\cdot\text{OH}$  or syrupy phosphoric acid in place of sulphuric acid. No sulphur dioxide is formed, and the reaction becomes in reality continuous. The method is only suitable for primary alcohols; secondary and tertiary under similar conditions yield olefines. Hydrochloric, hydrobromic, and hydriodic, among other acids, act similarly to sulphuric acid; thus ether is obtained when alcohol is heated with dilute hydrochloric acid in a sealed tube to  $180^\circ$ , ethyl chloride,  $\text{C}_2\text{H}_5\text{Cl}$ , being formed as an intermediate product. When alcohol is heated with hydrochloric acid, a state of equilibrium is established between the alcohol, ether, ethyl chloride, hydrochloric acid, and water, after which the same quantity of each of these products is destroyed as is formed in unit of time.

An interesting continuous process is passing absolute alcohol vapour over dehydrated alum at  $200^\circ$  (cf. also Chap. XLIX, D.).

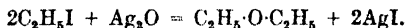
2. Certain complex ethers can be obtained by the direct union of an alcohol, e.g.  $\text{EtOH}$  with a tetra-alkylated olefine using sulphuric acid as catalyst:



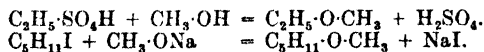
3. By the action of alkyl halides on sodium-alkyloxides (*Williamson*):



4. From alkyl halides and dry silver oxide, or mercuric oxide:



Modes of formation 1 and 3 yield mixed as well as simple ethers, e.g.:



*Properties*.—1. The ethers are very stable, e.g. ammonia, alkalis, dilute acids, and metallic sodium have no action upon them, nor has phosphorus pentachloride in the cold.

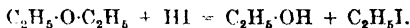
2. When superheated with water in presence of some acid, such as sulphuric, the ethers take up water and are retransformed into alcohols, the secondary more readily than the

primary; this change also proceeds, but extremely slowly, at the ordinary temperature.

3. When warmed with concentrated sulphuric acid, alcohol and ethyl hydrogen sulphate are formed:



4. When saturated with hydriodic acid gas at  $0^\circ$ , the ethers yield alcohol and alkyl iodide:



When the ethers are "mixed", the iodine attaches itself to the smaller alkyl group; further interaction yields, of course, two molecules of alkyl iodide.

5. When heated with phosphorus halides the oxygen atom is replaced by two halogen atoms, and two molecules of an alkyl halide are formed.

6. Like the alcohols, the ethers are oxidized by nitric and chromic acids, but halogens substitute in them and do not oxidize; in this latter respect they resemble the hydrocarbons.

7. Many ethers form definite compounds with acids, especially complex acids like  $\text{H}_4\text{FeC}_6\text{N}_6$  (B., 1901, 2688); also with bromine, with metallic salts, &c. (J. C. S., 1904, 1106; Proc. 1904, 165).

**Ethyl ether**, Ethane-oxy-ethane, "*Ether*" ( $\text{C}_2\text{H}_5$ )<sub>2</sub>O, was discovered by *Valerius Cordus* about 1544, and possibly before that time by *Raymond Lully*. It was also called "sulphuric ether", and "vitriol ether", on account of its being supposed to contain sulphur. Its composition was established by *Saussure* in 1807, and *Gay-Lussac* in 1815.

**Preparation.**—By the continuous process from ethyl alcohol and sulphuric acid at  $140^\circ$ , with gradual addition of the alcohol, according to *Boullay*. It is freed from alcohol by shaking with water, and dried by distillation over lime or calcium chloride, and finally over metallic sodium.

**Theories of the Formation of Ether.**—At first the action of the sulphuric acid was considered to consist in an abstraction of water. Later on, it was thought that the acid gave rise to a contact action (*Mitscherlich*, *Berzelius*), but *Liebig* showed that this view was incorrect, since ethyl hydrogen sulphate is formed. *Liebig* assumed that the ethyl hydrogen sulphate decomposed, when heated, into ether and  $\text{SO}_3$ ; but *Graham*, on the other hand, proved that the acid gives no ether when

heated alone to  $140^{\circ}$ , but only when heated with more alcohol.

After this, *Williamson* propounded the theory of etherification at present held, a theory based on the opinion of *Laurent* and *Gerhardt* that ether contains two ethyl radicals. Its correctness was proved by mode of formation 2, and also by the preparation of mixed ethers.

*Properties.*—It is a mobile liquid with powerful ethereal odour, and is very volatile, even at the ordinary temperature. It melts at  $-113^{\circ}$ , boils at  $+34.9^{\circ}$ , has specific gravity = 0.72 at  $17.4^{\circ}$ , and at  $120^{\circ}$  has a vapour pressure of 10 atmospheres. It produces considerable lowering of temperature when evaporated. It is easily inflammable, and therefore dangerous as a cause of fire, from the dissemination of its very heavy vapour; a mixture of it with oxygen or air is explosive. It is somewhat soluble in water (1 part in 10), and, conversely, 3 volumes of water dissolve in 100 volumes of ether; the presence of water can be detected by the milkiness which ensues upon the addition of carbon disulphide. Ether is an excellent solvent or extractive for many organic substances, and also for  $I_2$ ,  $Br_2$ ,  $CrO_3$ ,  $FeCl_3$ ,  $AuCl_3$ ,  $PtCl_4$ , and other chlorides. It forms crystalline compounds with various substances, e.g. the chlorides and bromides of Sn, Al, P, Sb, and Ti, being present in them as “ether of crystallization”.

When dropped upon platinum black it takes fire, and when poured into chlorine gas an explosion results, hydrochloric acid being set free. In the dark, however, and in the cold, substitution by chlorine is possible; the final product of the substitution, **perchloro-ether**,  $C_4Cl_{10}O$ , is solid and has an odour of camphor.

Ether was first employed as an anæsthetic by *Simpson* in 1848, but this property had been previously observed by *Faraday*. It is further used as an extractive in the colour industry, as *Hofmann's* drops when mixed with 1 to 3 volumes of alcohol, for ice machines, and for the preparation of colloidion, &c.

**Methyl ether**,  $(CH_3)_2O$  (*Dumas*, *Péligot*), closely resembles common ether, is gaseous at the ordinary temperature, but liquid under  $-20^{\circ}$ , and is prepared on the large scale for the production of artificial cold.

**Ethyl-cetyl- and dicetyl ethers** are solid at the ordinary temperatures.

Several ethers with unsaturated alcohol radicals are also

known, e.g. allyl ether,  $(C_3H_5)_2O$ , and vinyl-ethyl ether,  $C_2H_3 \cdot O \cdot C_2H_5$ . B.-pt.  $35.5^\circ$ . These can combine directly with bromine.

**Isomers.**—The general formula of the saturated ethers is  $C_nH_{2n+2}O$ . Isomeric with each ether is a saturated alcohol, thus  $C_2H_6O$  = methyl ether or ethyl alcohol,  $C_4H_{10}O$  = di-ethyl ether or butyl alcohol. From  $C_4H_{10}O$  on, however, several different isomeric ethers are not only possible, but are also known, e.g. di-ethyl ether,  $(C_2H_5)_2O$ , is isomeric with methyl-propyl ether,  $CH_3 \cdot O \cdot C_3H_7$ ; similarly methyl-amyl ether,  $CH_3 \cdot O \cdot C_5H_{11}$ , ethyl-butyl ether,  $C_2H_5 \cdot O \cdot C_4H_9$ , and dipropyl-ether,  $C_3H_7 \cdot O \cdot C_3H_7$ , are all isomeric. All these isomers belong to the same class (ethers) and differ only in the alkyl groups present. Such compounds are said to be *metameric*.

The determination of the *constitution* of the ethers is based upon (a) their syntheses according to modes of formation 1 or 3, and (b) their decomposition by HI according to reaction 4.

**Varieties of Isomerism.**—The cases of isomerism which have been mentioned up to now are of three kinds. The first was the isomerism of the higher paraffins, which, since it is based upon the dissimilarity of the carbon chains, is often termed **chain-isomerism**. The isomerism between ethylene and ethylidene chlorides or between primary and secondary propyl alcohols depends upon the differences in position of the substituting halogen or hydroxyl in the same carbon chain, and is termed **position isomerism**. In addition to these there is the third kind, **metamerism**. Further cases will be spoken of under the Benzene derivatives.

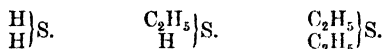
## B. Thio-alcohols and -ethers

The relationship between oxygen and sulphur, indicated by their positions in the periodic classification of the elements, is supported by a study of their carbon derivatives. Corresponding with the monohydric are the thio-alcohols or "thiols". Similarly a group corresponding with the ethers is known as the thio-ethers or alkyl sulphides. These are liquids of a most unpleasant and piercing odour, something like that of leeks; they are nearly insoluble in water, and the lower members are very volatile. The higher homologues are not so

soluble in water, but are soluble in alcohol and ether, and their smell is less strong on account of the rise in the boiling-point. They are readily inflammable.

The **thio-alcohols**, also called **mercaptans** or **alkyl hydro-sulphides**, e.g. mercaptan, ethan-thiol,  $\text{C}_2\text{H}_5\cdot\text{SH}$ , although of neutral reaction, possess the chemical characters of weak acids and are capable of forming salts, the "mercaptides", especially mercury compounds. The name "mercaptan" is derived from "corpus mercurio aptum". They are soluble in a strong solution of potash, and their boiling-points are distinctly lower than those of the corresponding alcohols. The **thio-ethers**, also termed **alkyl sulphides**, e.g. ethyl sulphide,  $(\text{C}_2\text{H}_5)_2\text{S}$ , are on the other hand neutral volatile liquids without acid character.

Both classes of compounds are derived from hydrogen sulphide by the replacement of either one or both atoms of hydrogen by alkyl groups, just as alcohol and ether are derived from water:

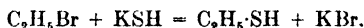


The boiling-points are methyl mercaptan  $6^\circ$ , ethyl mercaptan  $36^\circ$ , methyl sulphide  $37^\circ$ , ethyl sulphide  $92^\circ$ .

The *constitution* of these compounds follows at once from their modes of formation.

*Formation*.—The mercaptans may be obtained:

1. By warming an alkyl halide or sulphate with potassium hydrosulphide in concentrated alcoholic or aqueous solution:



2. By heating alcohol with phosphorus pentasulphide, the oxygen being thus replaced by sulphur (*Kekulé*).

The thio-ethers are similarly obtained:

1. From an alkyl halide or potassium alkyl sulphate and normal potassium sulphide:



2. By treating ethers with phosphorus pentasulphide.

"Mixed sulphides", comparable with the "mixed ethers", can also be prepared, e.g. methyl-ethyl sulphide,  $\text{C}_2\text{H}_5\cdot\text{S}\cdot\text{CH}_3$ .

**Mustard gas**, or  $\beta\beta'$ -dichloroethyl sulphide,  $(\text{CH}_2\text{Cl}\cdot\text{CH}_2)_2\text{S}$ .

was manufactured in large quantities by the following reaction for use as a poison gas during the war of 1914-18:

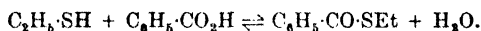


(Gibson and Pope, J. C. S., 1920, 271.)

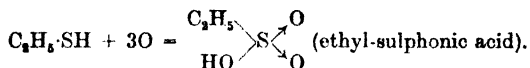
### Behaviour.—A. The Mercaptans.

1. Sodium and potassium act upon the mercaptans to form sodium and potassium salts, white crystalline compounds, which are decomposed by water. The mercury salts are obtained by warming an alcoholic solution of mercaptan with mercuric oxide, e.g. **mercuric mercaptide**,  $\text{Hg}(\text{C}_2\text{H}_5\text{S})_2$  (white plates). With mercuric chloride sparingly soluble compounds are formed, e.g.  $\text{C}_2\text{H}_5\text{S}\cdot\text{Hg}\cdot\text{Cl}$ , a white precipitate. The lead salts are yellow-coloured, and are formed when alcoholic solutions of a mercaptan and of lead acetate are mixed.

2. With acids they tend to form esters (thio-esters), but not so readily as the alcohols (*Reid*).



3. When oxidized with nitric acid the mercaptans are transformed into **alkyl-sulphonic acids** (isomeric with alkyl sulphites, Chap. IV, C4):



4. The mercaptans in the form of sodium salts are oxidized by iodine or by sulphuryl chloride,  $\text{SO}_2\text{Cl}_2$ , and also frequently in ammoniacal solution in the air to **disulphides**, e.g. **ethyl disulphide**,  $(\text{C}_2\text{H}_5)_2\text{S}_2$ , thus:



These are disagreeably-smelling liquids, which have much higher boiling-points than the mercaptans, and are formed by the putrefaction of certain proteins. They are reduced by nascent hydrogen, and with nitric acid yield **disulphoxides**, e.g. **ethyl disulphoxide**,  $(\text{C}_2\text{H}_5)_2\text{S}_2\text{O}_2$ .

**B. The Thio-ethers.**—1. They yield additive compounds with metallic salts, e.g.  $(\text{C}_2\text{H}_5)_2\text{S}$ ,  $\text{HgCl}_2$ , which can be crystallized from ether.

2. They are capable of combining with halogen or oxygen. Thus ethyl sulphide forms with bromine a **dibromide**,  $(\text{C}_2\text{H}_5)_2\text{S}\cdot\text{Br}_2$ , crystallizing in yellow octohedra, and with

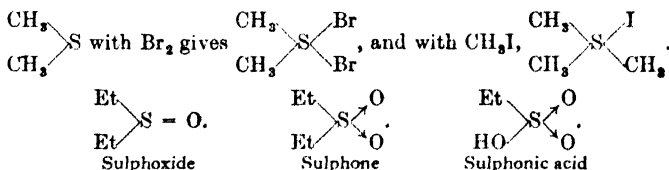
dilute nitric acid, **diethyl sulphoxide**,  $(C_2H_5)_2S:O$ , a thick liquid soluble in water, which combines further with nitric acid to the compound,  $(C_2H_5)_2SO$ ,  $HNO_3$ . Concentrated nitric acid or potassium permanganate oxidizes the sulphides or sulfoxides to **sulphones**, e.g. ethyl sulphide to **(di)-ethyl sulphone**,  $(C_2H_5)_2SO_2$ , and methyl-ethyl sulphide to **methyl-ethyl sulphone**,  $(CH_3)(C_2H_5)SO_2$ . The sulphones are solid well-characterized compounds which boil without decomposition.

The sulfoxides, but not the sulphones, are reduced by nascent hydrogen to sulphides.

3. The alkyl sulphides combine with alkyl iodides to form the **trialkyl-sulphonium iodides**, e.g.  $Me_2S$  and  $MeI \rightarrow Me_3SI$  (cf. ammonium salts). Trimethyl-sulphonium iodide is a colourless crystalline salt, soluble in water, and when heated is resolved into its components. It behaves exactly like a salt of hydriodic acid, and yields with moist silver oxide—but not with alkali—an oily base, **trimethyl-sulphonium hydroxide**,  $(CH_3)_3S \cdot OH$ , which cannot be volatilized without decomposition. This is as strong a base as caustic potash, and resembles the latter so closely that it absorbs carbon dioxide, cauterizes the skin, drives out ammonia, and gives salts with acids even with hydrogen sulphide; these latter closely resemble the alkali sulphides, e.g. they dissolve  $Sb_2S_3$  (*Oefele*, 1833; *Cahours*).

The compounds just described are of particular interest with regard to the question of the **valency of sulphur**.

The readiness with which these sulphur compounds are oxidized, and the ease with which they yield additive compounds, is undoubtedly due to the readiness with which the S atom passes from the di- to the tetra- or hexa-valent state.



Since in ethyl sulphide both the alkyl radicals are bound to the sulphur, this will also be the case in ethyl sulphone, otherwise the sulphones would manifestly be easily saponifiable. (See Ethyl-hydrogen sulphite.) The sulphonium hydroxides also can only be explained very insufficiently as

molecular compounds, on the assumption of the divalence of sulphur. The formula  $(\text{CH}_3)_2\text{S} + \text{CH}_3\text{OH}$  for trimethylsulphonium hydroxide does not indicate in the least the strongly basic character of this substance, since it is not explicable why the mere addition of the neutral methyl alcohol to the equally neutral methyl sulphide should produce such an effect.

With respect to **isomers**, the same general conditions prevail in the sulphur as in the corresponding oxygen compounds.

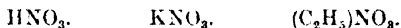
### SULPHIDES OF UNSATURATED ALKYL RADICALS

**Allyl sulphide.**  $(\text{C}_3\text{H}_5)_2\text{S}$  (*Wertheim*), 1844, present in the oil of *Allium sativum*—oil of garlic—in *Thlaspi arvense*, &c., may be prepared from allyl iodide and  $\text{K}_2\text{S}$  (*Hofmann, Cahours*). B.-pt.  $140^\circ$ .

Analogous **alkyl selenium** and **tellurium compounds** are also known. They are in part distinguished by their excessively disagreeable, nauseous, and persistent odour.

## C. Esters of the Alcohols with Inorganic Acids and their Isomers

The esters or alkyl salts may be considered as derived from the acids by the exchange of the replaceable hydrogen of the latter for alkyl radicals, just as metallic salts result by exchanging the hydrogen for a metallic radical:



Or they are derived from the alcohols by exchange of the hydroxyl radical for acid radicals, e.g.  $\text{C}_2\text{H}_5\cdot\text{NO}_3$ , ethyl nitrate;  $\text{C}_2\text{H}_5\cdot\text{SO}_4\text{H}$ , ethyl hydrogen sulphate; and  $\text{C}_2\text{H}_5\cdot\text{Cl}$ , ethyl chloride.

Monobasic acids yield only one kind of ester, "**neutral or normal esters**"—which are analogous to the normal metallic salts of those acids.

Dibasic acids yield two series of esters—(1) **acid esters** and (2) **neutral esters**—corresponding respectively with acid and normal salts; thus,  $\text{C}_2\text{H}_5\cdot\text{HSO}_4$  and  $(\text{C}_2\text{H}_5)_2\cdot\text{SO}_4$  are the acid and normal ethyl esters of sulphuric acid. Tribasic acids yield three series of esters, &c.

The composition of the esters or alkyl salts is therefore



exactly analogous to that of metallic salts, so that in the definition of polybasic acids their behaviour in the formation of esters may also be included.

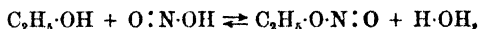
The normal esters are mostly liquids of neutral reaction, and often of very agreeable odour, with relatively low boiling-points, and volatilize, eventually in a vacuum, without decomposition. Most of them are very sparingly soluble in water. The acid esters, also called ester-acids, on the other hand, are of acid reaction, without smell, usually very readily soluble in water, much less stable than the neutral esters, and not volatile without decomposition. They act as acids, i.e. form salts and esters.

All esters are able to combine with water, and are by this means resolved again into their components, namely, alcohol and acid, e.g.:



This process occurs when the ester is boiled with alkalis or acids, or when heated with steam to over  $100^\circ$ , e.g.  $150^\circ$ – $180^\circ$ , and is termed **hydrolysis**, or *saponification*, when alkalis are used (see Soaps, p. 184). The reaction is usually conducted in a flask fitted with a reflux condenser, but with esters derived from strong acids the reaction takes place when the ester is mixed with water at the ordinary temperature.

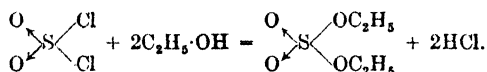
*General Modes of Formation.*—1. The simplest method for obtaining an ester is by the action of the acid on the alcohol, water always being formed as a by-product. As the reactions are reversible,



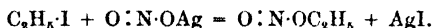
it is essential that the water formed should be removed from the sphere of action by the aid of concentrated sulphuric acid, fused zinc chloride, &c., or that a large excess of acid should be employed, otherwise after a short time a state of chemical equilibrium is reached, all four compounds are present, and the direct and reverse reactions are proceeding at the same rate; even prolonged heating will then not transform any further amounts of acid and alcohol into ester.

Esters are therefore often prepared by adding an excess of concentrated sulphuric acid to a mixture of the alcohol and sodium salt of the acid.

2. The alcohol is heated with the acid chloride, thus:



3. The silver salt of the acid is heated with an alkyl iodide; this is a method of very general application, although it often leads to isomers of the expected ester (see also p. 105):

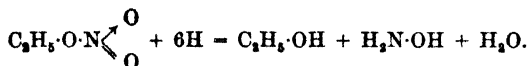


Besides the true esters, there are also included in this division several other classes of acid derivatives isomeric with them, but distinguished from them by not being readily hydrolysed, i.e. by being more stable, e.g. nitro-compounds, sulphonic and phosphinic acids, &c. The hydrocyanic derivatives of the alcohols will also be described here for the sake of convenience. These, also, are not hydrolysed in the normal manner into alcohol and acid, but are decomposed in quite a different manner.

## 1. ESTERS OF NITRIC ACID

**Methyl nitrate**,  $\text{CH}_3\cdot\text{O}\cdot\text{NO}_2$ , is a colourless liquid, boiling at  $66^\circ$ . **Ethyl nitrate**,  $\text{C}_2\text{H}_5\cdot\text{O}\cdot\text{NO}_2$  (*Millon*), is a mobile liquid of agreeable odour and sweet taste, but with a bitter after-taste; it boils at  $86^\circ$ , and burns with a white flame. Both esters are soluble in water. The latter is prepared directly from the alcohol and acid, with the addition of urea in order to destroy any nitrous acid as fast as it is formed.

Nitric esters contain a large proportion of oxygen in a form in which it is readily given up; they therefore explode when suddenly heated. They are very readily hydrolysed to nitric acid and the alcohol when boiled with alkalis. Tin and hydrochloric acid reduce them to hydroxylamine:



These two reactions indicate that the nitrogen atom is not directly united to carbon, as it is so readily removed either as nitric acid or as hydroxylamine.

## 2. DERIVATIVES OF NITROUS ACID

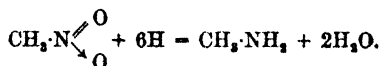
The compound  $C_2H_5O_2N$  exists in two isomeric forms, represented by the formulæ  $C_2H_5 \cdot O \cdot N : O$  and  $C_2H_5 - N \begin{smallmatrix} \nearrow O \\ \searrow O \end{smallmatrix}$ . The former is termed ethyl nitrite, as it is the true ester of nitrous acid,  $H \cdot O \cdot N : O$ ; the isomeride is termed nitro-ethane, as it contains the nitro group  $-N \begin{smallmatrix} \nearrow O \\ \searrow O \end{smallmatrix}$  attached to carbon.

**a. Alkyl nitrites.**—These are obtained by the action of nitrous fumes (from arsenious oxide and nitric acid), or of sodium nitrite and sulphuric acid, or of copper and nitric acid upon the alcohols. They are neutral liquids of aromatic odour, with very low boiling-points, and are readily hydrolysed to the corresponding alcohol and acid. When reduced they yield the alcohol, ammonia, and water.

**Methyl nitrite** is a gas. **Ethyl nitrite** boils at  $18^\circ$ , has a characteristic odour, and in the impure state, as obtained from alcohol, copper, and nitric acid, is used medicinally under the name of "sweet spirits of nitre".

**Amyl nitrite**,  $C_5H_{11} \cdot O \cdot N : O$ , is a pale yellow liquid boiling at  $96^\circ$ , and is used in medicine; it produces expansion of the blood-vessels and relaxation of the contractile muscles.

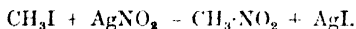
**β. The Nitro-derivatives** are colourless liquids of ethereal odour, practically insoluble in water, and boiling at temperatures some  $100^\circ$  higher than their isomers. Like the latter they distil without decomposition, and occasionally explode when quickly heated. They are fundamentally distinguished from the alkyl nitrites by not being readily hydrolysed, and by yielding amino-compounds (see these) on reduction, the nitrogen remaining attached to carbon:



**Nitro-methane** boils at  $99^\circ$ – $101^\circ$ . **Nitro-ethane**,  $C_2H_5 \cdot NO_2$  (*V. Meyer and Stüber*, 1872), boils at  $113^\circ$ – $114^\circ$ , burns with a bright flame, and the vapour does not explode even at a high temperature.

**Formation.**—1. The nitro-compounds may be obtained by

treating an alkyl iodide with solid silver nitrite (*V. Meyer*). When methyl iodide is used nitro-methane alone is formed, with ethyl iodide about equal weights of nitro-ethane and ethyl nitrite, and the higher homologues in regularly decreasing amounts as compared with those of their isomers, from which, however, they may be readily separated by distillation. Tertiary alkyl iodides do not yield nitro-compounds (cf. *Kohler*, J. A. C. S., 1916, 898; *Reynolds* and *Atkins*, 1929, 279). The latter show that the bromides react more readily than chlorides or iodides, and primary alkyl halides give better yields than secondary or tertiary:

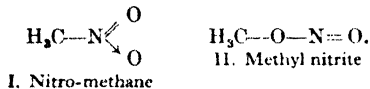


Nitro-methane is most readily prepared by the action of sodium nitrite solution on sodium chloro-acetate, carbon dioxide being eliminated.

2. The nitro-derivatives of the lower paraffins cannot be obtained by the direct action of nitric acid on the hydrocarbons, but with some of the higher derivatives this is possible, e.g. heptane, octane, &c. With decane a 30-per cent yield of a mono-nitro-derivative may be obtained by means of fuming nitric acid. (*Worstell*, Am. 1898, **20**, 202; 1899, **21**, 211; *Konowaloff*, Abs. 1905, i, 764; 1907, **1**, 1.) This method is largely employed in the aromatic series (see Nitrobenzene).

The constitution of the nitro-compounds follows from the facts given on p. 104, and it follows that the N atom is attached to C of an alkyl group.

With the alkyl nitrites both by hydrolysis and reduction nitrogen is eliminated as  $\text{HNO}_2$  or  $\text{NH}_3$  and hence is presumably attached to O and not to C (II).



From this follows for the hypothetical hydrated nitrous acid the formula  $\text{H}\cdot\text{O}\cdot\text{N}\cdot\text{O}$ , and for the anhydride the formula  $(\text{NO})_2\text{O}$ . The aromatic hydrocarbons, e.g. benzene,  $\text{C}_6\text{H}_6$ , yield with nitric acid nitro-compounds, thus:



Nitric acid, therefore, contains a nitro-group bound to hydroxyl, corresponding with the formula  $\text{H}\cdot\text{O}\cdot\text{NO}_2$ .

**Behaviour.**—1. They yield primary amines with acid reducing agents, e.g. iron and acetic acid, tin and hydrochloric acid, &c., substituted hydroxylamines being formed as intermediate products (V. Meyer, B., 1892, 1714).

2. **Primary** ( $\text{CH}_2\text{NO}_2$ ) and **secondary** ( $\text{CHNO}_2$ ) nitro-compounds can yield metallic derivatives, and hence possess certain acidic properties. For example, nitro-methane, and nitro-ethane react with alcoholic sodium hydroxide, yielding sodium compounds,  $\text{CH}_2\text{NaNO}_2$  and  $\text{CH}_3\text{CHNaNO}_2$ . It is almost certain that these sodium salts are not true derivatives of the nitro-compound, but are derived from an isomer, the

so-called *iso-nitro-compound*  $\text{CH}_2 \cdot \text{N} \begin{array}{c} \text{O} \\ \nearrow \\ \text{O} \cdot \text{H} \end{array}$ , and thus sodium

nitro-methane has the constitutional formula  $\text{CH}_2\text{:NO}\cdot\text{ONa}$  (Holleman, B., 1900, 2913). The nitro-derivatives are thus not true acids, but *pseudo acids* (Hantzsch, B., 1899, 577; see also Phenylnitromethane). These sodium salts are crystalline solids, and are highly explosive.

**Tertiary** nitro-compounds ( $\text{CNO}_2$ ) contain no hydrogen joined to the carbon atom which is united to the nitro-group, and they have not an acid character; the acidifying influence of the nitro-group does not therefore extend to those hydrogen atoms which are attached to other carbon atoms.

The hydrogen in the primary and secondary nitro-derivatives, which is attached to the same carbon atom as the  $\text{NO}_2$  group, can also be replaced by bromine. So long as hydrogen, as well as this bromine and the nitro-group, remains joined to the carbon atom in question, the compound is of a strongly acid character; but when this hydrogen also is substituted by bromine, the compound becomes neutral, e.g. dibromo-nitro-ethane,  $\text{CH}_3\text{CBr}_2\text{NO}_2$ , is neutral.

The reactivity of the hydrogen atoms of the  $\text{---CH}_2\text{NO}_2$  and  $\text{---CHNO}_2$  groups, characteristic of primary and secondary nitro-compounds, is exemplified in the reactions of these compounds with aldehydes in the presence of sodium carbonate. A primary nitro-compound can combine with one or with two molecules of formaldehyde, yielding  $\text{---CH(NO}_2\text{)CH}_2\cdot\text{OH}$  and  $\text{---C(NO}_2\text{)(CH}_2\cdot\text{OH)}_2$ .

3. The reactions of the nitro-compounds with nitrous acid is very varied. The primary yield **nitrolic acids** and the

secondary **pseudo-nitrols**, while the tertiary do not react with it at all. Thus from nitro-ethane,  $\text{CH}_3\cdot\text{C}\begin{array}{l} \text{H}_2 \\ \text{NO}_2 \end{array}$  **ethyl-**

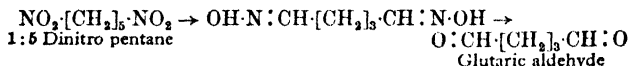
**nitrolic acid**,  $\text{CH}_3\cdot\text{C}\begin{array}{l} \text{N}\cdot\text{OH} \\ \text{NO}_2 \end{array}$  an acid crystallizing in light

yellow crystals and yielding intensely red alkali salts, is formed. Normal nitro-propane acts similarly. Secondary nitro-propane,  $(\text{CH}_3)_2\text{CH}\cdot\text{NO}_2$ , gives, on the contrary, **propyl-pseudo-nitrol**,  $(\text{CH}_3)_2\text{C}(\text{NO})(\text{NO}_2)$ , a white crystalline, indifferent, non-acid substance, which is blue either when fused or when in solution. These reactions, which are only given with compounds of low molecular weight (in the primary up to  $\text{C}_8$ , and in the secondary up to  $\text{C}_6$ ), are specially applicable for distinguishing between the primary, secondary, or tertiary nature of an alcohol (see p. 76). The nitro-hydrocarbons, which are readily prepared from the iodides, are dissolved in a solution of potash to which sodium nitrite is added, the solution acidified with sulphuric acid and again made alkaline, and then observed for the production of a red coloration (primary alcohol), a blue coloration (secondary alcohol), or no coloration (tertiary alcohol).

**Chloropicrin**,  $\text{CCl}_3\text{NO}_2$ , a heavy liquid of excessively suffocating smell, b.-pt.  $112^\circ$ , is formed from many hydrocarbon compounds by the simultaneous action of nitric acid and chlorine, chloride of lime, &c. It is best obtained from picric acid and bleaching-powder.

Polynitro-derivatives are also known. **Dinitromethane**,  $\text{CH}_2(\text{NO}_2)_2$ , an unstable yellow oil; **dinitroethane**,  $\text{CH}_3\cdot\text{CH}(\text{NO}_2)_2$ , obtained from  $\text{CH}_3\cdot\text{CHBr}\cdot\text{NO}_2$  and potassium nitrite, b.-pt.  $185^\circ$ ; **trinitromethane** or **nitroform**,  $\text{CH}(\text{NO}_2)_3$ , colourless crystals, m.-pt.  $15^\circ$ ; **tetranitromethane**,  $\text{C}(\text{NO}_2)_4$ , colourless crystals, m.-pt.  $13^\circ$  and b.-pt.  $126^\circ$ , is prepared by the action of nitric acid ( $D = 1.53$ ) on acetic anhydride (*Chattaway*, J. C. S., 1910, 2100), or by passing acetylene into nitric acid and a mercury salt, then warming with sulphuric acid and distilling (*Orton*). For constitution, cf. *Schmidt*, B., 1919, 400. Good yields (50 per cent) of dinitro-compounds of the type  $\text{NO}_2\cdot[\text{CH}_2]_n\cdot\text{NO}_2$  can be obtained from the corresponding di-iodo-derivatives and silver nitrite (*Von Braun and Sobecki*, B., 1911, 2526) provided  $n > 3$ . The compounds are stable

and react with bromine, nitrous acid, &c., in much the same manner as mono-nitro-compounds. They are accompanied by alkylene dinitrites,  $\text{O:N}\cdot\text{O}[\text{CH}_2]_n\cdot\text{O:N:O}$ , and nitro-nitrites,  $\text{NO}_2\cdot[\text{CH}_2]_n\cdot\text{O:N:O}$ , from which they can be separated by fractional distillation. The dinitro-compounds can be used for the preparation of dialdehydes, since when reduced with stannous chloride they yield dioximes, and these on hydrolysis give dialdehydes:



### 3. ESTERS OF SULPHURIC ACID

As a dibasic acid sulphuric acid can give rise to both **neutral** or **normal esters**, e.g.  $(\text{C}_2\text{H}_5)_2\text{SO}_4$ , and **acid esters** or **alkyl hydrogen sulphates**, e.g.  $\text{C}_2\text{H}_5\text{HSO}_4$ .

The neutral esters are formed by the three general methods: (a) from fuming sulphuric acid and alcohol; (b) from silver sulphate and alkyl iodide; (c) from sulphuryl chloride and alcohol:  $\text{SO}_2\text{Cl}_2 + 2\text{C}_2\text{H}_5\text{OH} = \text{SO}_2(\text{OC}_2\text{H}_5)_2 + 2\text{HCl}$ .

The acid esters of the primary alcohols are generally prepared directly from their components. Secondary and tertiary alcohols do not yield them.

**Ethyl sulphate**,  $(\text{C}_2\text{H}_5)_2\text{SO}_4$ , is a colourless oily liquid of an agreeable peppermint odour, insoluble in water, and solidifying on exposure to a low temperature. It boils at  $208^\circ$ , is quickly hydrolysed with boiling water, but only slowly with cold water, yielding alcohol and sulphuric acid. A 90-per-cent yield is obtained by distilling sodium ethyl sulphate in a vacuum.

**Methyl sulphate**,  $(\text{CH}_3)_2\text{SO}_4$ , is a syrupy oil, b.-pt.  $188^\circ$ , it is extremely poisonous, does not adhere to glass, and is a common reagent used instead of methyl iodide for the formation of methyl derivatives of phenols, alcohols, and amines, but only one methyl group reacts. It is also formed by the direct union of sulphur trioxide and methyl ether (E. P., 1919).

**Ethyl hydrogen sulphate**,  $\text{C}_2\text{H}_5\text{O}\cdot\text{SO}_2\cdot\text{OH}$  (*Dabit*, 1802), is obtained from a mixture of alcohol and sulphuric acid, but not quantitatively, on account of the state of equilibrium that ensues. It is also formed from ethylene and sulphuric acid at a somewhat higher temperature. It differs from sulphuric acid by its Ba-, Ca-, and Pb-salts being soluble, and it can

therefore be easily separated from the former by means of  $\text{BaCO}_3$ , &c. It yields salts which crystallize beautifully, e.g.  $\text{KC}_2\text{H}_5\text{SO}_4$ , but which slowly decompose into sulphate and alcohol on boiling their concentrated aqueous solution, especially in presence of excess of alkali.

These salts are frequently used instead of ethyl iodide for the preparation of other ethyl derivatives (process of ethylation).

The free acid ester is prepared by adding the requisite amount of sulphuric acid to the barium salt. It is a colourless oily liquid which does not adhere to glass, and which slowly hydrolyses when its solution is evaporated or kept. When heated alone it is decomposed into ethylene and sulphuric acid; with alcohol it yields ethyl ether and sulphuric acid. The sodium salts of the higher alkyl hydrogen sulphates, e.g.  $\text{CH}_3(\text{CH}_2)_n\cdot\text{CH}_2\cdot\text{O}\cdot\text{SO}_2\text{Na}$  are manufactured for use as detergents.

#### 4. DERIVATIVES OF SULPHUROUS ACID

**a. Alkyl Sulphites.**—**Ethyl sulphite**,  $\text{SO}_3(\text{C}_2\text{H}_5)_2$ , is an ethereal liquid of peppermint odour, which can be prepared from alcohol and thionyl chloride,  $\text{SOCl}_2$ , and which is rapidly hydrolysed by water. It has b.-pt.  $161^\circ$ , and its probable constitution is:  $\text{O}:\text{S}(\text{OEt})_2$ .

**Ethyl Hydrogen Sulphite.**—The very unstable potassium salt,  $\text{OEt}\cdot\text{SO}_2\text{K}$ , is formed by the action of dry sulphur dioxide on potassium ethoxide (*Rosenheim*, B., 1905, 1301). It is decomposed by water, yielding alcohol and potassium sulphite.

The action of sodium hydroxide on ethyl sulphite does not hydrolyse the ester to sodium ethyl sulphite, but to sodium ethyl sulphonate,  $\text{C}_2\text{H}_5\cdot\text{SO}_2\cdot\text{ONa}$ . (B., 1898, 406.)

**β. Sulphonic Acids.**—Sulphonic acids contain the univalent group  $\cdot\text{SO}_2\cdot\text{OH}$ . They are colourless oils or solids, extremely hygroscopic, readily soluble in water, and are strong monobasic acids. They are much more stable than the isomeric alkyl hydrogen sulphites; for example, they are not hydrolysed when boiled with aqueous alkalis or acids, but are decomposed when fused with potash. They are non-volatile with steam, and when strongly heated decompose.

**Ethyl-sulphonic acid**,  $\text{C}_2\text{H}_5\cdot\text{SO}_2\cdot\text{OH}$  (*Löwig*, 1839; *H. Kopp*, 1840), is a strong monobasic acid, and yields crystalline salts, e.g.  $\text{C}_2\text{H}_5\cdot\text{SO}_2\text{K} + \text{H}_2\text{O}$  (hygroscopic),  $\text{C}_2\text{H}_5\cdot\text{SO}_2\text{Na} + \text{H}_2\text{O}$ .

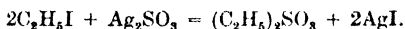


**Methyl-sulphonic acid**,  $\text{CH}_3\cdot\text{SO}_3\text{H}$ , is a syrupy liquid, and was prepared by *Kolbe* in 1845 from trichloro-methyl-sulphonic chloride,  $\text{CCl}_3\cdot\text{SO}_2\text{Cl}$  (produced from  $\text{CS}_2$ ,  $\text{Cl}_2$  and  $\text{H}_2\text{O}$ ).

*Modes of Formation*.—From sodium or ammonium sulphite and alkyl iodide:



Sulphonic esters are formed by the action of alkyl iodides on silver sulphite:



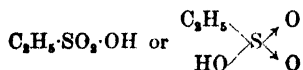
2. By the oxidation of mercaptans by  $\text{KMnO}_4$  or  $\text{HNO}_3$ :



The sulphonic acids yield chlorides with  $\text{PCl}_5$ , e.g. ethyl-sulphonic acid gives **ethyl-sulphonic chloride**,  $\text{C}_2\text{H}_5\cdot\text{SO}_2\text{Cl}$ , a liquid which boils without decomposition at  $177^\circ$ , fumes in the air, and is reconverted by water into ethyl-sulphonic and hydrochloric acids. Nascent hydrogen reduces it to mercaptan, and with zinc dust it yields the zinc salt of a syrupy, readily soluble acid, viz. **ethyl-sulphinic acid**,  $\text{C}_2\text{H}_5\cdot\text{SO}_2\text{H}$ , which may also be reduced to mercaptan. Sodium sulphinate yields ethyl sulphone when treated with ethyl bromide,  $\text{C}_2\text{H}_5\text{Br}$ . When esterified the acid forms an unstable ester, isomeric with ethyl sulphone (B., 1891, 2272).

**Ethyl Ethyl-sulphonate**,  $\text{C}_2\text{H}_5\cdot\text{SO}_2\cdot\text{OC}_2\text{H}_5$ , is isomeric with ethyl sulphite, and, being an ester of the more stable ethyl-sulphonic acid, can only be partially hydrolysed. It is prepared from silver sulphite and ethyl iodide. It boils at  $213^\circ$ , and the sulphonic esters generally have considerably higher boiling-points than the isomeric alkyl sulphites.

*Constitution*.—From the formation of the sulphonic acids from mercaptans by oxidation, and the (indirect) reversibility of this reaction, it follows that the sulphur in them is directly attached to the alkyl radical and ethyl-sulphonic acid has the constitution:



This constitution is in perfect harmony with the reaction of the acids with phosphorus pentachloride and also with their

monobasicity. The alkyl sulphites formed from thionyl chloride probably have the alkyl groups attached to oxygen, e.g. ethyl sulphite,  $\text{O}=\text{S}(\text{OEt})_2$ .

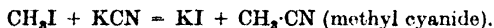
Esters of phosphoric acid  $\text{PO}(\text{OR})_3$ ,  $\text{PO}(\text{OR})_2(\text{OH})$ , and  $\text{PO}(\text{OR})(\text{OH})_2$ , ( $\text{R}$  = alkyl), exist, as do also similar compounds of phosphorous and hypophosphorous acids. The phosphinic acids, &c., are related to the two last-mentioned classes. Esters of boric silicic acids are also known.

### 5. ALKYL DERIVATIVES OF HYDROCYANIC ACID

Hydrocyanic acid,  $\text{HCN}$ , as a typical tautomeric substance (cf. Chap. LIII), yields two classes of derivatives by the exchange of its hydrogen atom for alkyl radicals, neither of which can be regarded as esters, in the sense that they are hydrolysed to the acid and alcohol.

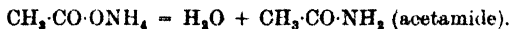
**a. Alkyl Cyanides or Nitriles,  $\text{R}\cdot\text{C}:\text{N}$ .**—These are either colourless liquids, which volatilize without decomposition, or solids with an ethereal odour slightly resembling that of leeks; they are lighter than water, and are relatively stable. The lower members are miscible with water, but the higher ones not, and they boil at about the same temperatures as the corresponding alcohols.

*Formation.*—1. By heating an alkyl iodide with an alcoholic solution of potassium cyanide, or potassium ethyl-sulphate with potassium ferrocyanide:

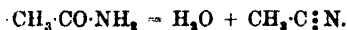


When other metallic cyanides are used the product is a mixture of an alkyl cyanide with the isomeric alkyl carbylamine and the proportions of the two vary largely with the metallic cyanide used (*Guillemard*, *Ann. Chim.*, 1908, (VIII), 14, 311).

2. From fatty acids, e.g. acetic acid,  $\text{CH}_3\cdot\text{CO}\cdot\text{OH}$ . The ammonium salt when distilled loses water and yields the acid amide, e.g.:



The amide when heated with a dehydrating agent, e.g.  $\text{P}_4\text{O}_{10}$ , loses a second molecule of water and yields the cyanide:



As a consequence of this mode of formation these compounds are also termed **nitriles** of the monobasic acids, e.g.  $\text{CH}_3\cdot\text{CN}$ , methyl cyanide or aceto-nitrile;  $\text{C}_2\text{H}_5\cdot\text{CN}$ , propionitrile, &c.

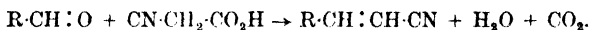
3. The higher nitriles, in which  $\text{C} > 5$ , are formed from the amides of acids of the acetic series containing 1 atom of carbon more in the molecule, and also from the primary amines with the same number of carbon atoms, upon treatment with bromine and caustic-soda solution. See Amides, Chap. VII, E.

4. From the oximes of the aldehydes, by warming with acetic anhydride. See Aldoximes, Chap. L, Cl.

5. In a few cases by the direct addition of  $\text{HCN}$  to an olefine

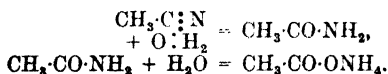


6. Unsaturated nitriles are formed by condensing cyano-acetic acid with an aldehyde:

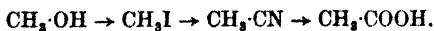


*Reactions.*—The nitriles are chemically active. Most of the reactions are of an additive nature, and are somewhat similar to those characteristic of the olefines. These reactions are in harmony with the constitutional formulæ usually attributed to the nitriles, e.g.  $\text{R}\cdot\text{C}:\text{N}$ , according to which a triple bond exists between a nitrogen and a carbon atom.

1. When hydrolysed with acids or alkalis, or superheated with water, they take up water (2 mols.) and yield the ammonium salts of fatty acids (with alkalis, the alkali salt, and free ammonia). The reaction undoubtedly proceeds in two distinct stages, and an acid amide is first formed;



It is generally impossible to stop the hydrolysis at the first stage in the case of aliphatic nitriles, but this is readily accomplished with aromatic cyanides. They are also hydrolysed by  $\text{H}_2\text{O}_2$ , and by catalytic hydrolysis in vapour phase by passing the nitrile and steam over heated thoria or alumina. This is a reaction of considerable interest, as it is thus possible to pass from a saturated alcohol,  $\text{C}_n\text{H}_{2n+1}\cdot\text{OH}$ , to the aliphatic acid,  $\text{C}_n\text{H}_{2n+1}\cdot\text{COOH}$ , which contains 1 atom of carbon more than the alcohol:

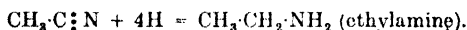


By using alcoholic sulphuric acid (10:1) as hydrolysing agent esters can be formed in place of acids (*Spiegel*, J. C. S., 1918, 216).

2. Hydrogen sulphide behaves similarly to water, yielding thio-acetamide  $\text{CH}_3\cdot\text{CS}\cdot\text{NH}_2$ .

3. By the addition of hydrochloric acid, amido-chlorides or imido-chlorides are formed; by the addition of ammonia bases, amidines, and by the action of alcoholic hydrogen chloride iminoethers  $\text{R}\cdot\text{C}(\text{OEt})\text{:NH}$ .

4. Primary amines are obtained by reducing nitriles with sodium and alcohol (p. 117; cf. *Rakshit*, J. A. C. S., 1913, 444).



Catalytic processes of hydrogenation give appreciable amounts of secondary amines, but by working in the presence of acetic anhydride it is possible to obtain pure acetyl derivatives of the primary amine (A., 1931, 485, 113).

5. Metallic potassium or sodium frequently induces polymerization; thus methyl cyanide yields in this way **cyanmethine**, a mono-acid base crystallizing in prisms.

**Aceto-nitrile**, *Ethane-nitrile*,  $\text{CH}_3\cdot\text{CN}$ , b.-pt.  $82^\circ$ , is present in the products of distillation from the vinasse of sugar beet and in coal-tar. **Propio-nitrile**, (*Propane-nitrile*),  $\text{C}_2\text{H}_5\cdot\text{CN}$ , **butyro-nitrile**,  $\text{C}_3\text{H}_7\cdot\text{CN}$ , and **valero-nitrile**,  $\text{C}_4\text{H}_9\cdot\text{CN}$ , are liquids of agreeable bitter-almond-oil odour; **palmito-nitrile**,  $\text{C}_{15}\text{H}_{31}\cdot\text{CN}$ , is like paraffin.

**$\beta$ . Isocyanides, Isonitriles or Carbylamines.**—These are colourless liquids readily soluble in alcohol and ether, but only slightly soluble in water. They have a feeble alkaline reaction, an unbearable putrid odour, and poisonous properties, and boil somewhat lower than the isomeric nitriles.

*Formation.*—1. By heating an alkyl iodide with silver cyanide instead of potassium cyanide (*Gautier*).

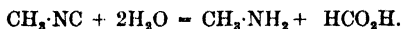
2. In small quantity, along with the nitrile, when a potassium alkyl-sulphate is distilled with potassium cyanide.

3. By the action of chloroform and alcoholic potash upon primary amines (*Hofmann*, 1869) (see pp. 68 and 119):



*Behaviour.*—1. The isonitriles differ fundamentally from the nitriles in their behaviour with water or dilute acids. When strongly heated with water, or with acids in the cold, they

decompose into formic acid and a primary amine containing an atom of carbon less than themselves:



Unlike the nitriles, they are very stable towards alkalis.

2. The isonitriles are also capable of forming additive products with the halogens,  $\text{HCl}$ ,  $\text{H}_2\text{S}$ , &c., compounds different from those given by the nitriles; thus, with  $\text{HCl}$  they yield crystalline salts which are rapidly decomposed by water into amine and formic acid.

3. Some of the isonitriles change into the isomeric nitriles when heated. According to *Wade* this change does not occur at all readily in the fatty series if the carbylamines are thoroughly dry. (J. C. S., 1902, 1596).

**Methyl isocyanide**,  $\text{CH}_3\cdot\text{NC}$ , boils at  $58^\circ$ , and **ethyl isocyanide**,  $\text{C}_2\text{H}_5\cdot\text{NC}$  at  $82^\circ$ .

*Constitution of the Nitriles and Isonitriles.*—The constitution of the nitriles follows from the readiness with which they can be hydrolysed to acids of the acetic series. In acetic acid we know that we have a methyl group directly attached to a carbon atom, e.g.  $\text{CH}_3\cdot\text{CO}\cdot\text{OH}$ , and since methyl cyanide on hydrolysis yields acetic acid, it also presumably contains the methyl group attached to carbon. The nitrogen atom, on the other hand, is eliminated, and is thus probably not directly bound to the alkyl radical. Consequently aceto-nitrile has the constitution  $\text{CH}_3\cdot\text{C}\equiv\text{N}$ .

This constitutional formula is supported by a study of the product formed on reduction, namely,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{NH}_2$ .

In the case of the isonitriles, however, it is the nitrogen which must be directly bound to the alkyl radical, as their close connexion with the amine bases shows, the amines being easily prepared from and reconverted into the isonitriles. The carbon atom of the cyanogen group, on the contrary, is eliminated as formic acid on decomposition with acid, and is consequently not directly united to the alkyl radical, but only through the nitrogen. The constitutional formula of an alkyl cyanide is best represented by the electronic structure



a structure supported by dipole moments and other physical properties. (*Sidgwick*, *The Covalent Link in Chemistry*, p. 187).

## D. Amines or Nitrogen Bases of the Alkyl Radicals

By the introduction of alkyl radicals in place of hydrogen into the ammonia molecule, the important class of **ammonia bases** or **amines** is formed.

The amines containing small alkyl groups bear the closest resemblance to ammonia, and are even more strongly basic than the latter. They have an ammoniacal odour, give rise to white clouds with volatile acids, combine with hydrochloric acid, &c., to salts with evolution of heat, and yield platini- and auri-chlorides. Their aqueous solutions precipitate insoluble hydroxides from solutions of the salts of the heavy metals, and these precipitates are frequently soluble in excess.

The lowest members of this class are combustible gases readily soluble in water. The next are liquids of low boiling-point, also at first readily soluble; but the solubility in water, and also the volatility, decrease with an increase in molecular weight, until the highest members of the series, such as tricetylamine,  $(C_{16}H_{33})_3N$ , are at the ordinary temperature odourless solids of high boiling-points, insoluble in water but soluble in alcohol and ether, and readily combining with acids to form salts. All amines are considerably lighter than water.

The quaternary ammonium hydroxides are solid and very hygroscopic, and closely resemble potash in properties.

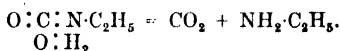
*Classification.*—The bases are divided into **primary, secondary, tertiary, and quaternary bases**, according as they contain 1, 2, 3, or 4 alkyl radicals; the three first are derived from ammonia, and the last from the hypothetical ammonium hydroxide,  $NH_4 \cdot OH$ . Characteristic of primary amines is the *amino* group,  $\cdot NH_2$ , of secondary, the *imino* group,  $:NH$ , and of tertiary, the N radical attached to three alkyl groups.

The system of *nomenclature* is simple, as indicated by the following examples:  $CH_3 \cdot NH_2$ , **methylamine**;  $C_3H_7 \cdot NH_2$ , **propylamine**;  $(C_2H_5)_2NH$ , **di-ethylamine**;  $(CH_3)_3N$ , **trimethylamine**; and  $N(C_2H_5)_4I$ , **tetraethylammonium iodide**.

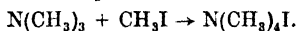
The alkyl radicals may be either saturated or unsaturated.

*Modes of Formation.*—1. Primary amines, e.g. methylamine, ethylamine, are obtained by heating alkyl cyanates with

potash solution (*Wurtz*, 1848), just as cyanic acid itself yields ammonia and carbon dioxide:



2. By the direct introduction of the alkyl radical into ammonia by heating a concentrated solution of the latter with methyl iodide, chloride, or nitrate, ethyl iodide, &c. In this reaction an atom of hydrogen is first exchanged for an alkyl radical, and the operation is repeated a second and third time so that  $\text{NH}(\text{CH}_3)_2$  and  $\text{N}(\text{CH}_3)_3$  are formed, the  $\text{HI}$  liberated forms salts with the  $\text{NH}_3$  and methylamines and finally the trimethylamine combines with  $\text{MeI}$ , forming tetramethylammonium iodide  $\text{NMe}_4\text{I}$ .



The compound obtained, tetramethylammonium iodide, is, however, no longer a salt of an amine, but of an ammonium base, and is not decomposed on distillation with potash solution. The velocities of formation of quaternary ammonium iodides from tertiary amines and alkyl iodides have been determined by *Menschutkin*. The reaction has been shown to be a bimolecular one. The velocity varies with the alkyl iodide employed, decreasing as the alkyl group becomes more complex. The solvent employed, for example, acetone, hexane, methyl alcohol, &c., also affects the velocity of formation to an enormous extent, e.g. the combination of ethyl iodide and tri-ethylamine takes place some 250 times as readily in ethyl alcohol as in hexane solution.

Primary and secondary bases can also be transformed into secondary and tertiary by warming with potassium alkyl-sulphates (*B.*, 1891, 1678), or alkyl sulphates and alkali.

When a mixture of alkyl iodides is used, **mixed amines**, i.e. amines containing different alkyl groups in the molecule, are obtained, e.g. **methyl-propylamine**,  $\text{NH}(\text{CH}_3)(\text{C}_3\text{H}_7)$ , **methyl-ethyl-propylamine**,  $\text{N}(\text{CH}_3)(\text{C}_2\text{H}_5)(\text{C}_3\text{H}_7)$ .

When a secondary or tertiary alkyl iodide is used some  $\text{HI}$  is eliminated and hence the product contains a certain amount of olefines.

The methylation (alkylation) of ammonia described above does not proceed in regular, well marked stages; the several processes go on simultaneously, the bases being partly liberated from the hydriodides by the ammonia, and so being free to

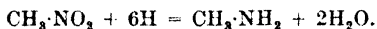
react with more alkyl halide. The product obtained by distillation with potash is therefore a mixture of all the three amines and ammonia.

These cannot be separated by fractional distillation, and one of the following methods is used: (a) *Hofmann's* method using ethyl oxalate,  $\text{OEt}\cdot\text{CO}\cdot\text{CO}\cdot\text{OEt}$ . Methylamine reacts with this ester to form chiefly (1) **dimethyl-oxamide**,  $\text{CH}_3\text{NH}\cdot\text{CO}\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_3$  (solid), and (2) some **methyl-oxamic ester**,  $\text{OEt}\cdot\text{CO}\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_3$  (liquid); dimethylamine yields (3) the **ethyl ester of dimethyl-oxamic acid**,  $\text{OEt}\cdot\text{CO}\cdot\text{CO}\cdot\text{N}(\text{CH}_3)_2$  (liquid), while trimethylamine does not react with the ethyl oxalate. The products can be largely separated by fractional distillation, the tertiary base passing over first, then 3 and 2, 1 being left in the flask. Each is separately decomposed with potash, (1) and (2) yielding methylamine, and (3) dimethylamine, cf. *Hibbert and Wise*, J. C. S., 1912, 344.

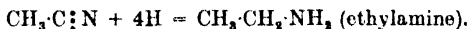
(b) *Hinsberg's* method, using an aromatic sulphonyl chloride (Chap. XXIII). The primary amine yields a product  $\text{R}\cdot\text{NH}\cdot\text{SO}_2\cdot\text{C}_6\text{H}_5$ , which has acidic properties owing to the NH group, the secondary amine forms the neutral compound  $\text{R}_2\text{N}\cdot\text{SO}_2\text{C}_6\text{H}_5$  insoluble in alkali, and the tertiary base does not react and is soluble in acid.

(c) A tertiary amine can be separated from a primary or secondary by treatment with a *Grignard* reagent.

3. The nitro-compounds yield primary amines when treated with acid reducing agents (see p. 106):



4. The nitriles, including hydrocyanic acid, are capable of taking up four atoms of hydrogen (see p. 113) and forming primary amines (*Mendius*, 1862):



5. Primary amines, in which  $\text{C} < 6$ , are prepared according to *Hofmann's* method, by the action of bromine and then of caustic-soda solution upon the amides of acids containing 1 carbon atom more than themselves (see Amides, Chap. VII, E.).

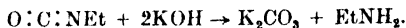
6. Primary amines likewise result from the reduction of the oximes or hydrazones (Chap. V, C.): for example, **acetaldoxime**:



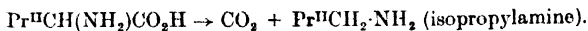


7. See Chap. XXVI, B., for *Gabriel's* method for preparation of primary amines from phthalimide.

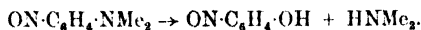
8. Esters of *isocyanic* acid on hydrolysis yield primary amines (*Würtz*, 1848):



9. Amino-acids are decarboxylated by certain bacteria to primary amines:



10. A convenient method for obtaining secondary amines is by hydrolysing a *p*-nitroso-di-alkylated aniline with alkali (Chap. XXI, C.):



11. Another method for secondary amines is by the action of an alkyl bromide on sodium cyanamide and hydrolysing the dialkylcyanamide:



*Isomers.*—Numerous isomers exist among the amines, thus:

	$\text{C}_2\text{H}_7\text{N}.$	$\text{C}_3\text{H}_9\text{N}.$	$\text{C}_4\text{H}_{11}\text{N}.$
Isomers {	$\text{NH}_2(\text{C}_2\text{H}_5)$ $\text{NH}(\text{CH}_3)_2$	$\text{NH}_2(\text{C}_3\text{H}_7)$ $\text{NH}(\text{CH}_3)(\text{C}_2\text{H}_5)$ $\text{N}(\text{CH}_3)_3$	$\text{NH}_2(\text{C}_4\text{H}_9)$ $\text{NH}(\text{CH}_3)(\text{C}_3\text{H}_7)$ and $\text{NH}(\text{C}_2\text{H}_5)_2$ $\text{N}(\text{CH}_3)_2(\text{C}_2\text{H}_5)$

This kind of isomerism is the same as that of the ethers (p. 97), i.e. metamerism. From  $(\text{C}_3\text{H}_7)$  onwards, isomerism can also occur in the alkyl radicals. According to theory, as many amines  $\text{C}_n$  as alcohols  $\text{C}_{n+1}$  are capable of existence.

*Behaviour.*—1. The amines combine directly with acids (organic or inorganic) to form **salts** in exactly the same way as ammonia; the quaternary ammonium bases, however, react with acids, forming salts and eliminating water like potassium or ammonium hydroxide:



The salts so obtained are white, crystalline compounds, readily soluble in water, and frequently hygroscopic. The chlorides form, with platinic chloride, sparingly soluble **plati-**

**chlorides** analogous to ammonium platinichloride,  $(\text{NH}_4)_2\text{PtCl}_6$ , e.g. methylamine platinichloride,  $(\text{CH}_3\text{NH}_2)_2\text{PtCl}_6$ .

The same applies to the **aurichlorides**, e.g.  $\text{C}_2\text{H}_5\text{NH}_2\text{AuCl}_4$ .

Strong alkalis, e.g. potassium hydroxide, decompose all the salts with the exception of the quaternary ammonium compounds yielding the free bases (and not ammonia).

They are stronger bases than ammonia, the strongest being the  $\text{NHR}_2$  compounds as determined by ionization constants, whereas the  $\text{NR}_3$  bases are somewhat weaker (J. C. S., 1912, 1671; *Werner*, B., 1918, 900; 1919, 1010).

Individual amines are often isolated and characterized as their picrates and sometimes as the picrolonates.

2. Hydrolysing agents such as alkalis and acids do not decompose the alkylated nitrogen bases.

3. The different classes of amines are distinguished from each other by the primary having 2 hydrogen atoms, the secondary 1, but the tertiary none replaceable by alkyl groups; the same applies to acyl groups, e.g. acetyl. The structure of a particular amine can often be determined by complete methylation and an analysis of the final salt, e.g. of the three isomeric amines  $\text{C}_3\text{H}_9\text{N}$ , propylamine gives with methyl iodide,  $\text{C}_3\text{H}_7\text{N}(\text{CH}_3)_3\text{I}$ , propyl-trimethyl-ammonium iodide =  $\text{C}_6\text{H}_{16}\text{NI}$ ; methyl-ethylamine gives  $\text{C}_2\text{H}_5\text{N}(\text{CH}_3)_3\text{I}$ , ethyl-trimethylammonium iodide =  $\text{C}_5\text{H}_{14}\text{NI}$ ; and trimethylamine gives  $\text{N}(\text{CH}_3)_4\text{I}$ , tetramethylammonium iodide =  $\text{C}_4\text{H}_{12}\text{NI}$ . An iodine estimation in the final product would immediately settle the structure of the original amine.

The primary bases further differ from the others in their behaviour with chloroform, carbon disulphide, and nitrous acid.

4. Only the primary bases react with chloroform and alcoholic potash, with formation of isonitriles (p. 113).

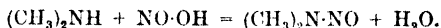
5. When warmed with carbon disulphide in alcoholic solution, the primary and secondary, but not the tertiary, bases react to form derivatives of thiocarbamic acids. (See Carbonic Acid Derivatives, Chap. XIII, D.) Should the amines be primary ones, the characteristically smelling isothiocyanates are produced upon heating the thiocarbamic derivatives with a solution of  $\text{HgCl}_2$  ("mustard oil" reaction. Cf. Chap. XXI, A.).

6. Nitrous acid reacts with the primary amines, forming alcohols, e.g.:



The reaction is not so simple with the higher homologues, as molecular rearrangements can occur, e.g. the formation of isopropyl alcohol from *n*-propylamine, and even elimination of water with the formation of an olefine (J. C. S., 1932, 3441).

Secondary bases yield with nitrous acid nitroso-compounds, e.g. "**dimethyl-nitrosamine**":



These nitrosamines are yellow-coloured volatile liquids of aromatic odour (*Geuther*) and give *Liebermann's* reaction with phenols (Chap. XXIV). When reduced with acid-reducing agents, or when heated with alcohol and hydrochloric acid, they regenerate the secondary amines. Weak reducing agents, however, convert them into hydrazines (this Chap. E.). The nitrosamines are frequently of great service in the purification of the secondary bases.

Nitrous acid forms salts with tertiary amines.

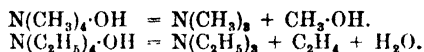
7. By the indirect action of nitric acid, **nitramines** result, i.e. amines in which an amino-hydrogen atom has been replaced by the nitro-group, e.g.  $\text{CH}_3\cdot\text{NH}\cdot\text{NO}_2$ , **methyl-nitramine**. Similarly, by the indirect introduction of an amino-group, hydrazines are formed, e.g.  $\text{CH}_3\cdot\text{NH}\cdot\text{NH}_2$ , methylhydrazine.

8. The primary and secondary amines readily react with acid chlorides and anhydrides yielding acyl derivatives (Chap. VII, B. and C.).

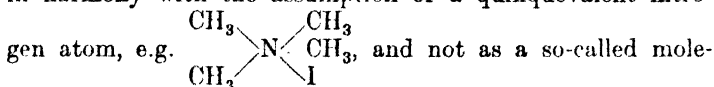
*m*-Nitrobenzene-sulphonyl chloride and toluene  $\omega$ -sulphonyl chloride are of value for characterizing particular secondary amines (J. A. C. S., 1925, 166; 1926, 2943).

9. While the amines are liberated from their salts by alkalis, the free bases of the quaternary ammonium salts, e.g. tetramethylammonium iodide, cannot be prepared from these by treatment with potash, because the products are soluble and non-gaseous, and hence an equilibrium is attained. The salts behave normally in aqueous solutions, for example, the iodides yield precipitates with silver nitrate, and are good electrolytes. The corresponding hydroxides, e.g.  $\text{N}(\text{CH}_3)_4\text{OH}$ , are obtained most readily by acting upon the iodides with moist silver oxide. These hydroxides are extraordinarily like caustic potash. They are colourless hygroscopic solids, readily soluble in water, and abstract carbon dioxide from the air. The solutions have strongly alkaline properties, are good electrolytes,

and precipitate metallic hydroxides from solutions of their salts. When distilled they decompose, yielding the tertiary base, the tetramethyl base yielding in addition methyl alcohol, and the homologous bases olefine and water (cf. *Ingold* and others, J. C. S., 1927-1933).



They are of importance for the study of the valency of nitrogen. Their formation and general properties are most in harmony with the assumption of a quinquevalent nitrogen atom, e.g.



(Cf. Trimethyl-sulphonium hydroxide.) The fact that the salts  $\text{N}(\text{CH}_3)_2(\text{C}_2\text{H}_5) + \text{C}_2\text{H}_5\text{Cl}$  and  $\text{N}(\text{CH}_3)(\text{C}_2\text{H}_5)_2 + \text{CH}_3\text{Cl}$  are identical, is in agreement with the former assumption. (*Meyer* and *Lecco*.) Lastly, optically active isomers are met with among the quaternary ammonium salts, a point which receives its readiest explanation from the dissymmetry of the cation containing a quadrivalent nitrogen atom. (See Chap. I, C2.)

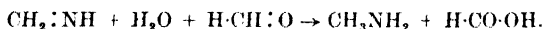
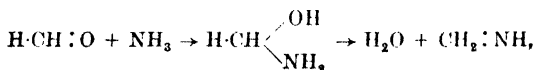
10. The quaternary iodides are resolved into tertiary base and alkyl iodide when heated. In a mixed salt the largest alkyl group is usually eliminated, the order being allyl, benzyl, ethyl, propyl, isoamyl, methyl (A., 1911, **382**, 5), and in certain cases an olefine and HI are formed.

The iodides form perbromides and iodides, e.g.  $\text{N}(\text{CH}_3)_4 \cdot \text{I} \cdot \text{I}_4$  (dark needles), and  $\text{N}(\text{C}_2\text{H}_5)_4 \cdot \text{I} \cdot \text{I}_2$  (azure-blue needles). Such periodides readily lose the excess of iodide, and are hence relatively unstable. Hepta- and ennea-iodides also exist.

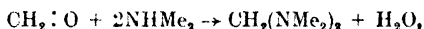
The following table gives the boiling-points of the various amines:

	Primary	Secondary	Tertiary
Methyl .. ..	-6°	7°	3.5°
Ethyl .. ..	19°	56°	90°
n-Propyl .. ..	49°	110°	156°
n-Butyl .. ..	76°	160°	215°
n-Octyl .. ..	176°	297°	366°

**Methylamines.** All three amines, particularly dimethylamine, are present in the brine in which herrings have been salted, and are derived from the decomposition of the fish. The secondary and tertiary amines are formed by the destructive distillation of the final residues from the molasses of beet-sugar factories. All three amines can be obtained from ammonia and formaldehyde (Werner, J. C. S., 1917, 844):



The formic acid can be further oxidized to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , or can be converted into methyl formate. Formaldehyde is thus a methylating agent, just as a mixture of  $\text{MeI}$  or  $\text{Me}_2\text{SO}_4$  and alkali. The methylamine can react with more formaldehyde, yielding dimethylamine, and the final stage is:



and above  $101^\circ$ :



no formic acid being produced.

When this method of formation of methylamines is used, the separation of the amines is based on the following facts: 1. Ammonium chloride is practically insoluble in a concentrated solution of methylamine hydrochloride. 2. Dimethylamine hydrochloride is more soluble in water than the monomethylamine salt, and the former is soluble in chloroform solution and the latter not.

**Methylamine**,  $\text{CH}_3\cdot\text{NH}_2$ , occurs in *Mercurialis perennis* and *annua* ("mercurialine"), in the distillate from bones and wood, and is formed when trimethylamine hydrochloride is heated at  $285^\circ$ .

It is most readily prepared from acetamide by the *Hofmann* reaction (No. 5, p. 117). Also from phthalimide (Chap. XXVI, B.) by methylating with formaldehyde and methyl alcohol at 70–90 atm. pressure and hydrolysing the methylphthalimide. It is more strongly basic and even more soluble in water than ammonia, has a powerful ammoniacal and at the same time fish-like odour, and burns with a yellowish flame. Its aqueous solution, like that of ammonia, precipitates many metallic

salts, frequently redissolving the precipitated hydroxides; unlike ammonia, it does not dissolve  $\text{Ni}(\text{OH})_2$  and  $\text{Co}(\text{OH})_2$ .

The **hydrochloride**,  $\text{CH}_3\cdot\text{NH}_2$ ,  $\text{HCl}$ , forms large glistening plates, is very hygroscopic and readily soluble in alcohol; the platinichloride crystallizes in golden scales, and the sulphate forms an alum.

**Dimethylamine**,  $(\text{CH}_3)_2\text{NH}$ , occurs in Peruvian guano and pyroligneous acid, and is formed by decomposing nitroso-dimethyl-aniline by caustic-soda solution.

**Trimethylamine**,  $(\text{CH}_3)_3\text{N}$ , is widely distributed in nature, being found in considerable quantity in *Chenopodium vulvaria*, also in *Arnica montana*, in the blossom of *Cratagus oxyacantha*, and of pear. It has an ammoniacal and fish-like odour.

The tertiary amines can be oxidized by means of hydrogen peroxide to compounds of the type  $(\text{CH}_3)_3\text{N}:\text{O}$ , **trimethylamine oxide**, which are colourless crystalline bases.

**Tetramethylammonium iodide**,  $\text{N}(\text{CH}_3)_4\text{I}$ , is obtained in large quantity directly from  $\text{NH}_3 + \text{CH}_3\text{I}$ . It crystallizes in white needles or large prisms, and has a bitter taste.

**Tetramethylammonium hydroxide**,  $\text{N}(\text{CH}_3)_4\text{OH}$ , crystallizes in hygroscopic needles, and can be obtained by the action of alcoholic potash on an alcoholic solution of its chloride; potassium chloride is precipitated, and the hydroxide remains in solution. It forms salts, e.g. a platinichloride, sulphide, polysulphide, cyanide, &c.

**Tetramethylammonium amalgam**,  $\text{Hg}(\text{NMe}_4)_x$ , is formed during the electrolysis of the chloride in absolute alcohol at  $-34^\circ$ , using a mercury cathode (J. A. C. S., 1911, 273).

**Ethylamines**. The ethylamines are usually manufactured from ethyl chloride and ammonia. Ethylamine can be obtained from ethylene and ammonia at  $450^\circ$  and 20 atm. pressure using a suitable molybdenum catalyst. They can be separated by fractional distillation, using a ten-bulb column (J. C. S., 1916, 174). For the preparation of mono- and di-ethylamine from ethylbromide and ammonia, and the separation of their hydrochlorides by ammonia, see Werner, J. C. S., 1918, 899.

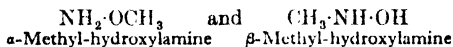
**Ethylamine**,  $\text{C}_2\text{H}_5\text{NH}_2$ , has a strongly ammoniacal smell and biting taste, mixes with water in every proportion, and burns with a yellow flame. It dissolves  $\text{Al}(\text{OH})_3$ , but not  $\text{Fe}(\text{OH})_3$ ; also  $\text{Cu}(\text{OH})_2$  with difficulty, but not  $\text{Cd}(\text{OH})_2$ . With bleaching powder it yields **ethyl-dichloro-amine**,  $\text{C}_2\text{H}_5\cdot\text{NCl}_2$ , as a yellow oil of a most unpleasant piercing odour.

**Tri-ethylamine**,  $(C_2H_5)_3N$ , is an oily strongly alkaline liquid. The precipitates which it gives with solutions of metallic salts are mostly insoluble in excess of the precipitant.

A compound of technical importance is the hydroxy-compound  $N(CH_2 \cdot CH_2 \cdot OH)_3$ , **triethanolamine**, a hygroscopic liquid forming neutral soaps with fatty acids which can be used as cleansing agents or for emulsifying oils (J. Ind.-Eng., 1930, 143).

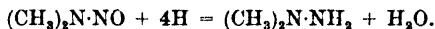
### E. Hydroxylamines; Hydrazines

The **Alkyl-hydroxylamines**, which are derived from hydroxylamine,  $NH_2 \cdot OH$ , just as the amines are from ammonia, belong to two different series, viz.:



The compounds of the first series, obtained from the oxime ethers (Chap. L, C1), are—as ethereal compounds—relatively stable, and do not reduce *Fehling's solution*. Those of the second series, obtained by the reduction of the nitro-hydrocarbons with zinc dust in ammonium chloride solution (p. 106), very readily undergo change, reduce *Fehling's solution* even in the cold, and yield primary amines when further reduced.

*E. Fischer* has given the name of **hydrazines** to a series of bases, mostly liquid and closely resembling the amines, but containing two atoms of nitrogen in the molecule, and differing from the latter especially by their capability of reducing *Fehling's solution*, for the most part even in the cold, and by the ease with which they are oxidized. They are derived from "Diamide" or "Hydrazine",  $NH_2 \cdot NH_2$  (*Curtius* and *Jay*, J. pr. Ch. 1889, (2), 39, 27), and are formed by the action of nascent hydrogen on the nitrosamines (p. 120):



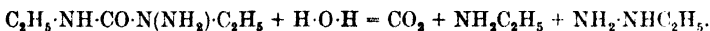
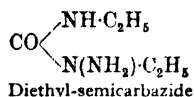
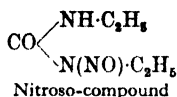
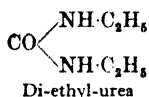
Primary, secondary, tertiary, and quaternary hydrazines are known, according as 1, 2, 3, or 4 of the hydrogen atoms in  $NH_2 \cdot NH_2$  are replaced by alkyl groups.

The secondary hydrazines exist in two isomeric forms, namely,  $NHR \cdot NHR$  and  $NH_2 \cdot NR_2$ , which are known respectively as *symmetrical* and *unsymmetrical* secondary hydrazines.

**Methyl-hydrazine**,  $CH_3 \cdot NH \cdot NH_2$  (cf. A., 1889, 253, 5). An

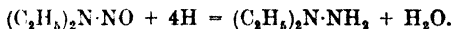
excessively hygroscopic liquid, which fumes in the air, and has an odour similar to that of methylamine. B.-pt.  $87^{\circ}$ .

**Ethyl-hydrazine**,  $C_2H_5 \cdot NH \cdot NH_2$ . When di-ethyl urea is treated with nitrous acid a nitroso-compound is formed, which, on reduction with zinc dust and acetic acid, yields the so-called "diethyl-semicarbazide", and this decomposes, when heated with hydrochloric acid, into carbon dioxide, ethylamine, and ethyl-hydrazine:



Ethyl-hydrazine is a colourless mobile liquid of ethereal and faintly ammoniacal odour, boiling at  $100^{\circ}$ . It is very hygroscopic, forms white clouds with moist air, dissolves in water and alcohol with evolution of heat, and corrodes cork and caoutchouc.

**Diethyl-hydrazine**,  $(C_2H_5)_2N \cdot NH_2$ , is prepared from diethylamine by transforming it into diethyl-nitrosamine by the nitrous-acid reaction, and then reducing the latter. It resembles ethyl-hydrazine closely:



**Tetra-ethyl-tetrazine**,  $(C_2H_5)_2 : N : N : N : N : (C_2H_5)_2$ , a colourless, strongly basic oil, volatile with steam, is formed when diethyl-hydrazine is heated with mercuric oxide.

The *constitution* of the hydrazines follows from their modes of formation. Since in diethyl-nitrosamine,  $(C_2H_5)_2N \cdot NO$ , for instance, the nitroso-group NO must be attached to the nitrogen of the amine and not to the carbon, judging from the ease with which it can be separated (p. 120), so the same linking of the atoms must be assumed in the hydrazines, which are formed from the nitroso-compounds by reduction, i.e. by exchange of O for 2H. The readiness with which diethyl-hydrazine is oxidized to diethylamine, e.g. by alkaline cupric oxide, is an agreement with such a formula. The hydrazines are relatively stable towards reducing agents.



## F. Diazo- and Triazo-compounds

**A. Diazo- or diazene compounds.**—By the action of nitrous acid on a solution of a salt of a primary aromatic amine of the type of aniline, the important group of diazo or diazonium salts is formed (Chap. XXII, A.). It is generally stated that aliphatic amino-compounds and aromatic amines of the type of benzylamine differ from the true aromatic amines in this respect, and immediately yield the corresponding hydroxy-compounds. A few aliphatic amino-compounds do, however, yield diazo-derivatives with cold nitrous acid; one of the best known of

these compounds is **ethyl diazo-acetate**,  $\begin{array}{c} \text{N} \\ \diagup \\ \parallel \\ \diagdown \\ \text{N} \end{array} \text{CH} \cdot \text{CO}_2\text{Et}$ , a

yellow oil, b.-pt. 141°. It differs from the aromatic diazonium salts in having both nitrogen atoms attached to carbon, and may be regarded as the anhydride of a diazo hydroxide,  $\text{OH} \cdot \text{N} : \text{N} \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et}$ . Not all aliphatic amines can yield diazenes; the essentials are that the carbon atom to which the amino group is united shall have a hydrogen atom attached to it, and also an unsaturated group, e.g. CO, CN. If these conditions are not fulfilled, no diazene can be isolated, and the product is an alcohol. Thus ethyl  $\alpha\beta$ -diaminopropionate with nitrous acid yields ethyl  $\alpha$ -diazo- $\beta$ -hydroxypropionate

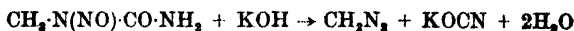


It is probable that the  $\text{H}_2$  of the  $\cdot\text{NH}_2$  reacts with the O of  $\text{O} : \text{N} \cdot \text{OH}$  yielding water and giving a diazo hydroxide,  $\cdot\text{N} : \text{N} \cdot \text{OH}$  which then loses water giving the diazene.

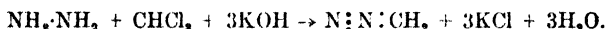
The simplest aliphatic diazo-compound is **diazo-methane**,

$\text{CH}_2 \begin{array}{c} \text{N} \\ \diagup \\ \cdot \\ \diagdown \\ \text{N} \end{array}$ , which may be regarded as the anhydride of  $\text{CH}_3 \cdot$

$\text{N} : \text{N} \cdot \text{OH}$ . Diazo-methane is prepared by decomposing nitrosomethyl-urethane,  $\text{CH}_3 \cdot \text{N}(\text{NO}) \cdot \text{CO}_2\text{Et}$ , with alkali, the compound,  $\text{CH}_3 \cdot \text{N} : \text{N} \cdot \text{OK}$ , being formed as an intermediate product (*Hantzsch and Lehmann*, B., 1902, 897), or still more readily by decomposing nitrosomethylcarbamide with potassium hydroxide

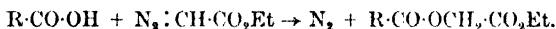


(Werner, J. C. S., 1919, 1093). A third method is by the action of chloroform and alkali on hydrazine

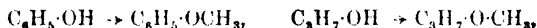


Both diazomethane and ethyl diazoacetate are extremely reactive and are of value as synthetical reagents.

1. With any organic acid or with dry hydrogen halides the H of the acid becomes replaced by  $\text{CH}_3$  or  $\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ . The products in the former case are methyl esters and in the latter case methyl esters with a  $\cdot\text{CO}_2\text{Et}$  group replacing one of the methyl hydrogen atoms.

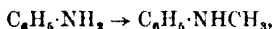


2. With aqueous solutions of mineral acids the  $\text{N}_2$  is replaced by H and OH forming in the one case methyl alcohol and in the other ethyl glycolate,  $\text{OH}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OEt}$  (Chap. IX, A.). Phenols and alcohols react with diazomethane yielding methyl ethers



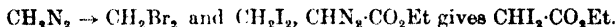
but the reaction with alcohols is slow.

Primary arylamines, e.g. aniline, react with diazomethane, yielding monomethyl derivatives



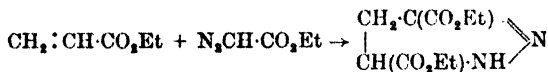
and diazomethane is an extremely valuable methylating agent.

3. Both compounds react with bromic or iodine, the  $\text{N}_2$  group being replaced by  $\text{Br}_2$  or  $\text{I}_2$ , e.g.:



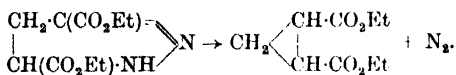
4. With acyl chlorides (acid chlorides, Chap. VII, B.) esters of ketonic acids are formed, e.g. acetyl chloride,  $\text{CH}_3\cdot\text{CO}\cdot\text{Cl}$ , and ethyl diazoacetate yield aceto-diazoacetic ester  $\text{CH}_3\cdot\text{CO}\cdot\text{CN}_2\cdot\text{CO}_2\text{Et}$  and ethyl chloroacetate.

5. They readily combine with unsaturated esters giving pyrazoline derivatives (Chap. XLII, A.):



(Büchner and others, A., 1892, 273, 214; V. Pechmann, B., 1898,

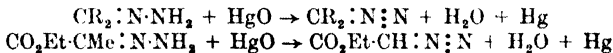
2950), and this pyrazoline when heated loses nitrogen and yields a derivative of cyclopropane (Chap. XVI):



6. When reduced with hydrogen and colloidal platinum the diazenes yield hydrazones, e.g.  $\text{CPh}_2\text{N}_2$  yields  $\text{CPh}_2\text{:N}\cdot\text{NH}_2$  (Helv., 1921, 21).

7. With thioketones, e.g.  $\text{Ph}_2\text{C:S}$ , the hydrocarbon diazenes yield an unstable compound  $\begin{array}{c} \text{CPh}_2\text{:S} \\ | \\ \text{CH}_2\text{:N} \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{N}$ , which loses nitrogen, giving tetraphenylethylene sulphide,  $\begin{array}{c} \text{CPh}_2 \\ | \\ \text{CPh}_2 \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{S}$  (Helv., 1920, 833).

Numerous homologues of diazomethane and of ethyl diazoacetate have been prepared by *Staudinger* (B., 1916, 1884), some by the oxidation with  $\text{HgO}$  of the hydrazones derived from aldehydes and ketones



and diazoparaffins by the decomposition of nitroso-urethanes.  $\text{CMe}_2\text{:N}_2$  is red and  $\text{CPh}_2\text{:N}_2$ , m.-pt.  $29^\circ$ , is bluish-red.

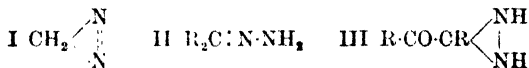
B. **Triazo-compounds.**—Forster (J. C. S., 1908, 72, 669, 1070, 1174, 1859, 1865) has obtained a number of fairly simple aliphatic triazo-derivatives containing the univalent

grouping,  $\begin{array}{c} \text{N} \\ || \\ \text{N} \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{N}\cdot$ . *Ethyl triazo-acetate*,  $\text{N}_3\cdot\text{CH}_2\cdot\text{CO}_2\text{C}_2\text{H}_5$ , ob-

tained by the action of sodium azide,  $\text{NaN}_3$ , on an alcoholic solution of ethyl chloro-acetate, is a colourless liquid, b.-pt.  $44^\circ\text{--}46^\circ$  under 2 mm. pressure, and has a sweet odour suggestive of chloroform. From this ester *triazio-acetic acid*, m.-pt.  $16^\circ$ , and almost as strong an acid as bromo-acetic, and *triazio-acetamide*, m.-pt.  $58^\circ$ , have been obtained by the ordinary methods. *Triazo-acetone*, acetonyl-azoimide,  $\text{N}_3\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_3$ , obtained from chloro-acetone, is a colourless liquid, b.-pt.  $54^\circ$  under 2 mm. pressure. It has the properties of a ketone, e.g. yields a semicarbazone, m.-pt.  $152^\circ$ , and is instantly decomposed by alkalis. *Ethyl  $\alpha$ -triazio-propionate* and the isomeric

$\beta$ -compound, have been prepared, and also  $\alpha$ -triazo-propionic acid,  $\text{CH}_3\cdot\text{CHN}_3\cdot\text{CO}_2\text{H}$ , the last of which has been resolved into optically active components. *Ethyl- $\beta$ -triazo-propionate* is so readily decomposed by alkalis that the corresponding acid and amide have not been prepared. *Allyl-azoimide*,  $\text{CH}_2\text{:CH}\cdot\text{CH}_2\cdot\text{N}_3$ , b.-pt.  $76\cdot5^\circ$ ; *triazo-ethyl alcohol*,  $\text{N}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , b.-pt.  $60^\circ/8\text{ mm.}$ ; *triazo-acetaldehyde*, an oil, together with numerous esters derived from triazo-ethyl alcohol, have been prepared. Bis-triazo-compounds can be obtained, e.g. *bis-triazo-ethane*,  $\text{N}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{N}_3$ , and *ethyl bis-triazo-acetate*,  $\text{CH}(\text{N}_3)_2\cdot\text{CO}_2\text{Et}$ , but are extremely explosive. Triazo-malonic acid and ethyl triazo-acetoacetate appear to be incapable of existence, but substituted derivatives, e.g.  $\text{CH}_3\cdot\text{CO}\cdot\text{CN}_3\text{Me}\cdot\text{CO}_2\text{Et}$ , and even a bis-triazo-compound,  $\text{CH}_3\cdot\text{CO}\cdot\text{C}(\text{N}_3)_2\cdot\text{CO}_2\text{Et}$ , are known. *Triazo-ethylene*,  $\text{N}_3\cdot\text{CH}\text{:CH}_2$ , can be obtained by eliminating hydrogen iodide from triazo-ethyl iodide. It is a pale-yellow liquid, b.-pt.  $26^\circ$ , and yields an oily dibromide. Numerous aromatic triazo-compounds have also been prepared, mainly from diazonium salts. (Cf. J. C. S., 1907, 855, 1350; 1909, 183; 1910, 126, 254, 1056, 1360, 2570.)

Differences of opinion on the structure of the diazene molecule still exist. (Cf. *Sidgwick*, J. C. S., 1929, 1108; 1933, 406. Also B., 1930, 702, and *Waters*, p. 110. The cyclic formula I was first suggested by *Curtius* and *Lang* (J. pr., 1892, [2], 44, 554) mainly because the hydrazones of  $\alpha$ -diketones differ in properties from the hydrazones of simple ketones; the latter were represented by an open chain structure II, and the former by ring formulae III, and as these give diazenes on oxidation the cyclic structure of the diazenes seemed probable.

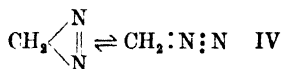


The examination of their absorption spectra by *Hantzsch* and *Lifschitz* (B., 1912, 3022) tended to confirm the ring structure. The non-cyclic structure of the hydrazones derived from  $\alpha$ -diketones has been rendered highly probable by the work of *Forster* and *Zimmerli* (J. C. S., 1910, 2156) on camphor quinone,

a typical  $\alpha$ -diketone,  $\text{C}_{18}\text{H}_{14} \begin{array}{c} \nearrow \text{CO} \\ | \\ \searrow \text{CO} \end{array}$ , which yields two isomeric

monohydrazones. These resemble one another so closely in chemical properties that they are undoubtedly stereoisomeric (geometrical isomerides) and therefore must be represented by the open chain structure, as the cyclic formula does not admit of stereoisomerism due to the nitrogen part of the molecule. Hence the diazenes derived from the hydrazones have open chain formulæ (IV), as represented by *Angeli* and supported by *Thiele* (B., 1911, 2522).

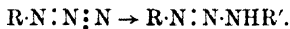
The possibility of an extremely rapid tautomeric change



must not, however, be forgotten.

Practically all the chemical reactions of diazenes are in harmony with the open chain structure. This contains a quinquevalent nitrogen atom, and not the ordinary azo group as in diazobenzene; this group is generally reactive, yet in the numerous reactions of the aliphatic diazo-compound such a group does not take part (cf. *Forster* and *Cardwell*, J. C. S., 1913, 861; also *Staudinger*, B., 1916, 1884).

In a similar manner hydrazoic acid and its derivatives are represented by open chain formulæ, e.g.  $\text{HN} \vdots \text{N} \vdots \text{N}$ . Such a structure accounts for the fact that by the action of *Grignard* reagents azides yield diazo-amino-compounds:



Parachors, on the other hand, are distinctly in favour of the cyclic structure (*Lindemann* and *Thiele*, B., 1928, 1529, cf. however, *Sidgwick*, J. C. S., 1929, 1108.)

**Carbon pernitride**,  $\text{CN}_4$ ,  $\text{N} \vdots \text{C} \cdot \text{N} \vdots \text{N} \vdots \text{N}$ , is formed by the action of cyanogen bromide on sodium azoimide. It forms colourless needles melting at  $36^\circ$ , explodes at  $170^\circ$ – $180^\circ$ , and its aqueous solution rapidly hydrolyses to hydrazoic acid and carbon dioxide (C. R., 1912, **154**, 1232).

**Carbon subnitride**,  $\text{C}_3\text{N}_2$ , obtained by heating tetraiodoglyoxalin (Chap. XLII, B.) at  $420^\circ$ , is a brown-black amorphous substance, and in many respects resembles animal charcoal (B., 1913, 3129).

## G. Alkyl Derivatives of Phosphorus, Arsenic, &amp;c.

## 1. PHOSPHORUS

Just as amines are derived from ammonia, so from phosphuretted hydrogen,  $\text{PH}_3$ , are derived **primary**, **secondary**, and **tertiary phosphines** by the exchange of hydrogen for alkyl radicals, and to these must likewise be added quaternary compounds, the **phosphonium bases**. The phosphines correspond closely with the amines in composition and in some of their properties, e.g. they are not saponifiable. But they differ from them in the following points:

1. Like phosphuretted hydrogen itself, the alkyl phosphines are only feebly basic; thus ethyl phosphine does not affect litmus, and its salts are decomposed by water. The salts of the secondary and tertiary compounds are not decomposed, thus showing that the presence of alkyl radicals tends to strengthen the basic properties of the compound.

2. Like phosphuretted hydrogen they are readily inflammable, and they are consequently rapidly oxidized in the air and readily take fire of themselves.

3. As the phosphorus atom in these compounds shows a tendency to pass from the ter- to the quinque-valent state, many of the phosphines behave as unsaturated compounds; they combine with oxygen, sulphur, halogens, &c., for example,  $(\text{CH}_3)_3\text{PO}$ ,  $(\text{CH}_3)_3\text{PS}$ ,  $(\text{CH}_3)_3\text{PCl}_2$ , and a compound  $(\text{CH}_3)_3\text{P}$ ,  $\text{CS}_2$ , in the form of red plates. The products obtained on oxidation are characteristic, and may be regarded as derived from phosphoric acid,  $\text{O}:\text{P}(\text{OH})_3$ , by the replacement of one or more OH groups by one or more alkyl radicals.

$\text{CH}_3\cdot\text{PH}_2$ , with nitric acid, yields  $\text{CH}_3\cdot\text{PO}(\text{OH})_2$ , **methyl-phosphonic acid**.

$(\text{CH}_3)_2\text{PH}$ , with nitric acid, yields  $(\text{CH}_3)_2\cdot\text{PO}\cdot\text{OH}$ , **dimethyl-phosphinic acid**.

$(\text{CH}_3)_3\text{P}$ , on oxidation in the air, yields  $(\text{CH}_3)_3\text{PO}$ , **trimethyl-phosphine oxide**.

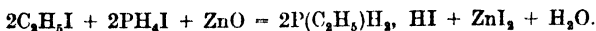
4. Corresponding with the disagreeable smell of phosphuretted hydrogen, they possess an excessively strong stupefying odour; thus ethyl phosphine has a perfectly overpowering smell, and excites on the tongue and deep down in the throat an intensely bitter taste.

*Formation*.—The tertiary phosphines and quaternary com-

pounds are formed directly from phosphine and an alkyl iodide. (Cf. Amines, formation 2).



2. According to *Hofmann* (1871), primary and secondary phosphines are formed by heating phosphonium iodide and an alkyl iodide with zinc oxide, e.g.:



They can be separated from one another by decomposing the salts of the primary phosphines by water, as already mentioned.

3. The tertiary phosphines are produced from calcium phosphide and an alkyl iodide, a reaction first observed by *Thenard* in 1846.

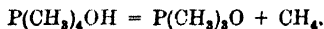
4. Also from phosphorus trichloride and zinc methyl, or magnesium alkyl iodides (*Auger and Billy*, C., 1904, **139**, 597).

5. The phosphonium salts are formed by the combination of tertiary phosphines with an alkyl haloid, and closely resemble the corresponding ammonium compounds.

**Tri-ethyl phosphine**,  $\text{P}(\text{C}_2\text{H}_5)_3$ , has no alkaline reaction. When concentrated it possesses a stupefying, and when dilute a pleasant hyacinth-like odour.

It forms a *peroxide*,  $\text{PEt}_3\text{O}_2$ , which is a powerful oxidizing agent, and hence tri-ethylphosphine can be used as an oxygen carrier, e.g. for the oxidation of indigotin by air.

**Tetramethyl-phosphonium hydroxide**,  $\text{P}(\text{CH}_3)_4\text{OH}$ , yields trimethyl-phosphine oxide and methane when heated:



## 2. ARSENIC

The similarity of arsenic to phosphorus and nitrogen is further exemplified by the analogous compounds which it forms with alkyl radicals. In virtue, however, of the more metallic character of arsenic, it does not show the same tendency to combine with alkyl radicals and hydrogen at the same time, but forms derivatives containing alkyl groups and electro-negative elements like chlorine or oxygen. Arsenic analogues of methylamines have been prepared, and are very unstable. (*Dehn*, Am. C. J., 1905, **33**, 120.) Trimethyl-arsine, analogous to trimethylamine and trimethyl-

phosphine, is well known. Examples of **primary and secondary compounds** are methyl-arsine dichloride,  $\text{CH}_3\cdot\text{AsCl}_2$ , dimethyl-arsine chloride,  $(\text{CH}_3)_2\text{AsCl}$ , and analogous substances. They are colourless liquids of stupefying odour, exerting in some cases an unbearable irritating action upon the mucous membrane. They do not possess basic properties. In addition to these there exist also quaternary compounds, **arsonium salts**, which are analogous to the quaternary phosphonium salts.

The halogen of the chlorine compounds is easily replaceable by its equivalent of oxygen. Thus, corresponding with the compound  $\text{R}\cdot\text{AsCl}_2$  there is an oxide  $\text{R}\cdot\text{AsO}$  and a sulphide  $\text{R}\cdot\text{AsS}$ , and with the chloride  $\text{R}_2\text{AsCl}$  an oxide  $(\text{R}_2\text{As})_2\text{O}$ . These oxides, liquid or solid, are compounds of stupefying odour, and behave like basic oxides; hydrochloric acid reconverts them into the corresponding chlorides.

Here, also, the tendency of arsenic to change from the trivalent to the quinquevalent state is especially marked. The above chlorides and trimethyl-arsine itself all combine with two atoms of chlorine to compounds of the type  $\text{AsX}_5$ . The above oxygen compounds of the type  $\text{AsX}_3$  and also trimethyl-arsine are consequently oxidizable to compounds containing one O atom or two OH groups more, acids or oxides which are also formed from the chlorides of the type  $\text{AsX}_5$  by exchange of halogen for O or OH, e.g. cacodyl oxide,

$(\text{Me}_2\text{As})_2\text{O}$ , to cacodylic acid,  $\text{Me}_2\text{As} \begin{smallmatrix} \text{OH} \\ \diagup \\ \text{O} \end{smallmatrix}$ . These products

are therefore completely analogous to the phosphonic and phosphinic acids and phosphine oxides already described.

The compounds  $\text{As}(\text{CH}_3)_x\text{Cl}_{5-x}$ , of the type  $\text{AsX}_5$ , when heated, decompose into methyl chloride and compounds  $\text{As}(\text{CH}_3)_{x-1}\text{Cl}_{4-x}$ , of the type  $\text{AsX}_3$ , this elimination of methyl chloride taking place the more readily the fewer methyl groups are present in the molecule; thus  $\text{As}(\text{CH}_3)_3\text{Cl}_2$  breaks up when somewhat strongly heated,  $\text{As}(\text{CH}_3)_2\text{Cl}_3$  at  $50^\circ$ , and  $\text{As}(\text{CH}_3)\text{Cl}_4$  at  $0^\circ$ , i.e. the last-named is only stable when in a freezing-mixture. When, therefore, chlorine acts upon  $\text{As}(\text{CH}_3)\text{Cl}_2$  at the ordinary temperature, the reaction appears to be one of direct exchange of alkyl for chlorine, thus:





The *tertiary arsines* are formed:

1. From sodium arsenide and alkyl iodide (*Cahours* and *Riche*):

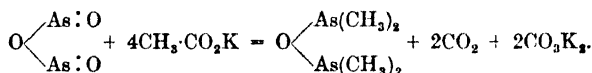


2. From arsenious chloride and (a) zinc alkyl (*Hofmann*), or (b) magnesium alkyl halide (*Pfeiffer*, B., 1904, 4620; *Sauvage*, C., 1904, 139, 674; *Hibbert*, B., 1906, 160).

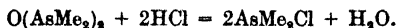
**Trimethyl-arsine**,  $\text{As}(\text{CH}_3)_3$ , and **triethyl-arsine**,  $\text{As}(\text{C}_2\text{H}_5)_3$ , are liquids sparingly soluble in water. They fume in the air, and are thereby oxidized to tri-methyl- or -ethyl-arsine oxide.

Tri-methyl-arsine is formed by the action of certain moulds, especially *Penicillium brevicaulis* on a mixture containing carbohydrate and an arsenite or arsenious oxide. The same organism has the power of methylating both sulphur and selenium compounds (Chap. LXIX, C.).

The **secondary arsines** are obtained from cacodyl and cacodyl oxide, which are formed when a mixture of potassium acetate and arsenious oxide is distilled (*Cadet*, 1760):



The distillate of cacodyl and cacodyl oxide so obtained, and termed "alkarsin", fumes in the air and is spontaneously inflammable (*Cadet's* "fuming arsenical liquid"). Hydrochloric acid acts upon it to form cacodyl chloride (*Bunsen*, 1838), and caustic-potash solution gives pure **cacodyl oxide**,  $\text{As}_2(\text{CH}_3)_4\text{O}$ , a liquid of stupefying odour which produces nausea and unbearable irritation of the nasal mucous membrane; it boils without decomposition, and is insoluble in water and of neutral reaction. It yields salts with acids, e.g. **cacodyl chloride** with hydrochloric acid:



The chloride is a liquid of even more stupefying odour and violent action than the oxide, and its vapour is spontaneously inflammable. When heated with zinc clippings in an atmosphere of carbon dioxide, it yields the free **cacodyl**,  $\text{As}_2(\text{CH}_3)_4$  (from *κακώδης*, "stinking"), a colourless spontaneously inflammable liquid insoluble in water and boiling undecomposed at 170°, and with a nauseous odour which produces vomiting

Cacodyl plays, therefore, the part of a simple electro-positive element; it is a true "organic element" (*Bunsen*).

**Cacodylic acid**,  $\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} > \text{As} \begin{array}{c} \text{O} \\ \text{OH} \end{array}$ , is crystalline, soluble in

water, odourless, and poisonous. It forms crystallizable salts.

For more complex Arsenic Compounds see Chap. LXVI.

## SUMMARY

		Compounds with Chlorine	Oxides	Acids
Primary	Methyl- arsine dichloride, $\text{AsMeCl}_2$ , B.-p. $133^\circ$ .	Methyl- arsine tetra- chloride, $\text{AsMeCl}_4$ .	Methyl- arsine oxide, $\text{AsMeO}$ , B.-p. $95^\circ$ .	Methyl- arsonic acid, $\text{O}:\text{AsMe}(\text{OH})_2$ , Solid plates.
Secondary	Cacodyl chloride, $\text{AsMe}_2\text{Cl}$ , B.-p. $100^\circ$ .	Cacodyl trichloride, $\text{AsMe}_3\text{Cl}_3$ .	Cacodyl oxide, $(\text{AsMe}_2)_2\text{O}$ , B.-p. $150^\circ$ .	Cacodylic acid, $\text{O}:\text{AsMe}_2\cdot\text{OH}$ , Prisms, M.-p. $200^\circ$ .
Tertiary	Trimethyl- arsine, $\text{AsMe}_3$ , B.-p. $70^\circ$ .	Trimethyl- arsine dichloride, $\text{AsMe}_3\text{Cl}_2$ .	Trimethyl- arsine oxide, $\text{AsMe}_3\text{O}$ , Solid.	

## 3. ANTIMONY, BORON, AND SILICON COMPOUNDS

Alkyl derivatives of antimony are also known, e.g. **Trimethylstibine**, a spontaneously inflammable liquid with a garlic odour; **Antimony pentamethyl**,  $\text{SbMe}_5$ , a non-poisonous volatile liquid; and **Tetramethylstibonium hydroxide**,  $\text{SbMe}_4\cdot\text{OH}$ , a solid resembling caustic potash. Mixed derivatives, e.g.  $\text{SbEt}_2\text{Ph}$  and  $\text{SbEtPh}_2$  can be obtained by heating the mixture of  $\text{SbCl}_3$  and  $\text{SbPh}_3$ , first forming  $\text{SbPhCl}_2$  and  $\text{SbPh}_2\text{Cl}$ , and then treating these with magnesium ethyl bromide. The trialkyl-derivatives of bismuth, e.g.  $\text{BiMe}_3$ , are unstable, and bismuthonium compounds are not known.

**Boron tri-ethyl**,  $\text{B}(\text{C}_2\text{H}_5)_3$  (*Frankland*), is a spontaneously inflammable liquid which burns with a green flame with deposition of much soot; and **boron trimethyl**,  $\text{B}(\text{CH}_3)_3$ , an analogous gas of an unbearable stinking smell.

The silicon compounds (*Friedel and Crafts*), in contradistinction to the foregoing, resemble methane and the paraffins rather than the spontaneously inflammable silicon hydride, and are very stable in the air. **Tetramethyl silicane**,  $\text{Si}(\text{CH}_3)_4$ , is a mobile liquid similar to pentane, and floats on water. **Tetraethyl silicane** or **Silicononane**,  $\text{SiEt}_4$ , is also known, and gives rise to numerous derivatives corresponding with those of tetraethyl methane, e.g.  $\text{SiC}_8\text{H}_{19}\text{Cl}$ ,  $\text{SiC}_8\text{H}_{19}\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ ,  $\text{SiC}_8\text{H}_{19}\cdot\text{OH}$ , **Silicononyl alcohol**, &c. Cf. Chap. L, B., and for nomenclature, *Kipping*, J. C. S., 1912, 423. Numerous organic derivatives of silicon have been described by *Kipping* during the years 1901–1929.

## H. Organo-Metallic Compounds: Grignard Reagents

Most of the important metals form definite compounds with alkyl groups. The composition of these organo-metallic or metallo-organic compounds almost always corresponds with that of the metallic chlorides from which they are derived by the replacement of halogen by alkyl. They are colourless, mobile liquids which boil, without decomposition, at relatively low temperatures; they often decompose violently with water and burn explosively in the air, but in other cases they are stable, both in water and air. To the former category belong the magnesium, zinc, and aluminium alkyls, and to the latter the mercury, lead, and tin compounds. As most of the compounds are volatile, their molecular weights can be determined, as the alkyl radicals are monovalent. Examples are:  $\text{ZnMe}_2$ ,  $\text{CdMe}_2$ ,  $\text{HgEt}_2$ ,  $\text{AlMe}_3$ ,  $\text{PbMe}_4$ ,  $\text{SnEt}_4$ , &c.

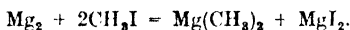
The physical and chemical properties of these compounds favour their covalent structure, e.g. the zinc in  $\text{ZnMe}_2$  has an outer shell of four electrons.

Compounds are also known which contain halogen as well as alkyl radicals combined with a metal, e.g.  $\text{CH}_3\cdot\text{Mg}\cdot\text{Br}$ . They are known as *Grignard* compounds. They behave like salts. The halogen in them can be replaced by hydroxyl, whereby basic compounds result, compounds which are often much more strongly basic than the corresponding metallic hydroxides, in accordance with the electro-positive character of the alcohol radical. Such hydroxides or oxides cannot be volatilized

without decomposition. Compounds of the type,  $\text{CH}_3\cdot\text{Mg}\cdot\text{I}$ , are very readily prepared from their components ( $\text{Mg} + \text{CH}_3\text{I}$ ) in dry ethereal solution, and are largely made use of as synthetic reagents.

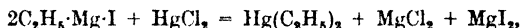
The organo-metallic compound may be prepared:

1. By treating the alkyl halide with the metal in question. In this way zinc-, magnesium-, and mercury-alkyls are got:



The mixed organo-metallic compounds (p. 139), e.g.  $\text{CH}_3\cdot\text{Mg}\cdot\text{I}$  or  $\text{C}_2\text{H}_5\cdot\text{Zn}\cdot\text{I}$ , are probably formed as intermediate products.

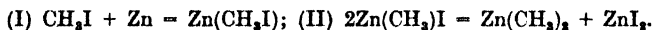
2. Numerous metallic compounds have been prepared by double decomposition between zinc-alkyl and the metallic chlorides, or more recently by the action of the mixed magnesium compounds on the metallic chloride. *Pfeiffer* (B., 1904, 319, 1125, 4617,) *Hibbert* (B., 1907, 160) have prepared numerous tin, lead, and mercury compounds by this method:



and a compound  $\text{Pb}(\text{C}_6\text{H}_5)_3$  analogous to triphenylmethyl (Chap. LII, B1), has also been isolated (B., 1919, 2165). *Kipping* has used Grignard reagents for synthesizing various organo-silicon compounds (J. C. S., 1907-1915).

**Potassium- and Sodium methyl**,  $\text{K}(\text{CH}_3)$  and  $\text{Na}(\text{CH}_3)$ , **Potassium- and Sodium ethyl**,  $\text{K}(\text{C}_2\text{H}_5)$  and  $\text{Na}(\text{C}_2\text{H}_5)$ , and similar derivatives, e.g. sodium benzyl,  $\text{Na}\cdot\text{CH}_2\cdot\text{C}_6\text{H}_5$ , are formed by the action of the alkali metal on the corresponding mercury compound in dry benzene. They are mostly colourless amorphous solids and burn in contact with the air. The benzyl compound is a red crystalline compound and its ethereal solution is an electrolyte (*Schlenck* and *Holz*, B., 1917, 262). They combine with carbon dioxide, yielding the alkali salts of carboxylic acids.

**Zinc methyl or methide**,  $\text{Zn}(\text{CH}_3)_2$  (*Frankland*, 1849), is prepared according to method 1:



The first stage is completed upon warming, and the second upon distilling the resulting product. The zinc is conveniently used in the form of the "copper-zinc couple", and the reaction is facilitated by the addition of ethyl acetate, the reason for this not being known. Zinc methyl is a colourless, mobile,

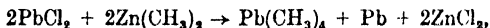
strongly refracting liquid of very piercing and repulsive smell. B.-pt.  $46^{\circ}$ ; sp. gr. 1.39. It is spontaneously combustible and burns with a brilliant reddish-blue flame (the zinc flame), with formation of zinc oxide, but may be distilled in an atmosphere of carbon dioxide. When the supply of oxygen is limited, zinc methoxide,  $\text{Zn}(\text{OCH}_3)_2$ , is formed. It reacts violently with water, yielding methane and  $\text{Zn}(\text{OH})_2$ , and with methyl iodide gives ethane. It is employed in the preparation of secondary and tertiary alcohols and of ketones. Iodine converts it into **zinc-methyl iodide**,  $\text{ZnCH}_3\text{I}$ , white plates (see above), and methyl iodide; an excess of iodine yields zinc iodide and methyl iodide.

**Zinc ethyl**,  $\text{Zn}(\text{C}_2\text{H}_5)_2$  b.-pt.  $118^{\circ}$ , sp. gr. 1.18, closely resembles zinc methide.

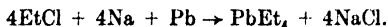
The mercury compounds,  $\text{HgMe}_2$  and  $\text{HgEt}_2$ , are produced by method of formation 1, also by method 2. They are colourless liquids of peculiar sweetish and unpleasant odour, and boil respectively at  $95^{\circ}$  and  $159^{\circ}$ . They are permanent in the air, but inflammable, and both—especially the methyl compound—are very poisonous.

**Aluminium methyl**,  $\text{Al}(\text{CH}_3)_3$ , is spontaneously inflammable and decomposes violently with water. B.-pt.  $130^{\circ}$ .

**Lead tetraethyl** is formed according to method 2, with separation of lead:



or on large scale by the action of ethyl chloride at a high temperature on an alloy of sodium and lead:



It is stable in the air and is mixed with petrol (1 in 1000) to prevent knocking (pre-ignition) in internal-combustion engines. The **hydroxide**,  $\text{Pb}(\text{CH}_3)_3\cdot\text{OH}$ , forms pointed prisms, smells like mustard, and is a strong alkali; thus, it saponifies fats, drives out ammonia from its salts, precipitates metallic salts, &c. The compound  $\text{Pb}_2(\text{C}_2\text{H}_5)_6$  is also known.

The tin compounds are similar (*Ladenburg, Frankland*).

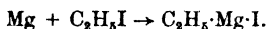
**Tin tetramethyl**,  $\text{Sn}(\text{CH}_3)_4$ , **Tin tetraethyl**,  $\text{Sn}(\text{C}_2\text{H}_5)_4$ , **Tin triethyl**,  $\text{Sn}_2(\text{C}_2\text{H}_5)_6$ , **Tin dimethyl**,  $\text{Sn}_2(\text{CH}_3)_4$ , &c., are of interest as indicating the quadrivalence of tin.

## GRIGNARD REAGENTS •

For a number of years the zinc alkyl compounds were of considerable importance, as they were used for synthesizing different types of carbon compounds, more particularly hydrocarbons, secondary and tertiary alcohols and ketones, and the structural formulæ given to products were largely based on these syntheses.

Since 1900 the metallic alkyls have been almost completely replaced by the mixed organo-magnesium compounds introduced by *Grignard* (C. R., 1900, **130**, 1322; 1901, **132**, 558), and hence commonly known as *Grignard* reagents. They are of enormous value in Synthetic Chemistry. Analogous aluminium compounds,  $\text{RAlCl}_2$  and  $\text{R}_2\text{AlCl}$ , are also used (J. Org. 1940, 106).

The reagents are prepared by dissolving dry magnesium ribbon or filings in a dry ethereal solution of an alkyl bromide or iodide:

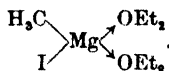


Aromatic compounds in which halogen is attached either to the side chain or nucleus react in a similar manner (cf. Chap. XIX, B.) and even unsaturated halides can be used in presence of a carbonyl compound (B., 1922, 2754, 2770), but dihalides are very rarely used.

For effects of small amounts of impurities cf. J. S. C. I., 1934, 214T, also J. A. C. S., 1929, 1579.

In many cases it is not necessary to prepare the actual *Grignard* compound; a mixture of the alkyl or aryl halide and magnesium with dry ether is added to the reagent on which it is to react (*Davies and Kipping*, J. C. S., 1911, 296).

The *Grignard* reagent does not exist as such in the ethereal solution, but in the form of an additive compound with ether, i.e.  $\text{MgCH}_3\text{I}$ ,  $2(\text{C}_2\text{H}_5)_2\text{O}$ . This additive compound can be isolated by removing the ether and warming the residue under reduced pressure at  $100^\circ$ , and is relatively stable, and can be represented by the co-ordinate structure:

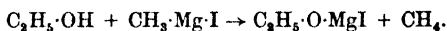


The alkyl magnesium halides are also formed when benzene

• F. Runge, *Organo-magnesium Verbindungen* (Stuttgart, 1932).

is used, but a much higher temperature is required, and a trace of ether or of a tertiary amine accelerates the reaction.

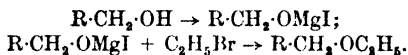
The *Grignard* reagents react readily with water or with alcohols yielding hydrocarbons and a compound  $R \cdot O \cdot MgI$ :



Based on this reaction, a process has been worked out for estimating hydroxy groups in carbon compounds (*Hibbert* and *Sudborough*, J. C. S., 1904, 933; *Zercwetinoff*, B., 1907, 2023), and consists in measuring the volume of methane evolved. In a somewhat similar manner the reaction may be used for differentiating primary, secondary, and tertiary amines, as the first contains two, the second one, and the last no reactive hydrogen atoms in their molecules (*Sudborough* and *Hibbert*). With  $H_2O_2$  a *Grignard* reagent yields the corresponding alcohol, e.g. isobutyl or isoamyl alcohol.

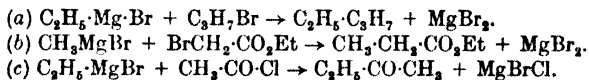
As synthetic reagents the *Grignard* compounds may react in one of three ways:

1. With reactive hydrogen atoms, e.g. in  $\cdot OH$ ,  $\cdot COOH$ ,  $\cdot NH_2$ ,  $\cdot NHR$ ,  $\cdot CH$ , or the hydrogen atom of a reactive methylene group. The product formed from an alcohol and a *Grignard* reagent can, by the action of an alkyl halide, yield an ether:



If a primary or secondary amine is used and the product treated with methyl sulphate, the N-methyl derivative of the amine is formed.

2. With the halogen atom of an alkyl halide, halogenated ester or an acid chloride.



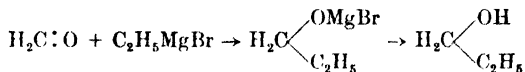
In reaction (a) the hydrocarbon often contains an olefine (J. A. C. S., 1918, 833; J. C. S., 1931, 3057).

As a rule the reaction (c) does not stop at the formation of the ketone, but proceeds further as described under 3.

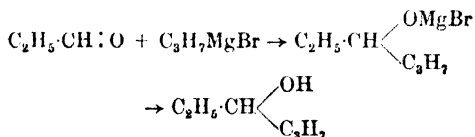
3. The addition of  $CH_3$  and  $MgI$  to unsaturated linkings; the commonest of these is the addition to the  $\cdot C:O$ , carbonyl group, but can also occur at  $C:C$ ,  $C:N$ , &c.

The syntheses of alcohols—primary, secondary, and tertiary—are based on the addition of the *Grignard* to a carbonyl group and the reaction of the product with water or a dilute acid.

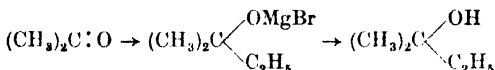
(a) With formaldehyde  $\text{H}\cdot\text{CH}:\text{O}$ , the product is a primary alcohol:



(b) With other aldehydes the product is a secondary alcohol:



(c) With a ketone the product is a tertiary alcohol:



with the exception of certain  $\alpha\alpha$ -substituted ketones when secondary alcohols are formed (Annales, 1921, IX, **16**, 354).

Tertiary alcohols are also formed from acid chlorides or esters and a *Grignard* reagent (cf. p. 80). In these reactions it is probable that ketones are first formed by the exchange of the Cl of the acid chloride or the OEt of the ester for the alkyl group of the *Grignard* reagent.

It is clear that if dialdehydes, diketones, or esters of dibasic acids are used dihydric alcohols (glycols) will be formed.

In the preparation of an alcohol, especially in the aromatic series, it frequently happens that an olefine hydrocarbon is formed instead of the alcohol, especially when a high temperature is used, and is to be attributed to the elimination of  $\text{Br}\cdot\text{Mg}\cdot\text{OH}$  from the additive compound of the ketone or aldehyde and *Grignard* reagent (cf. Chap. XVIII, B.).

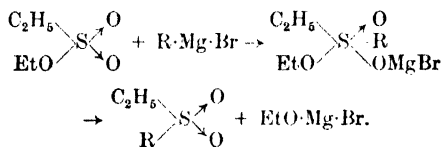
*Grignard* reagents are extremely useful for preparing the alkyl and aryl derivatives of many metals and non-metals, (cf. p. 137), by the reaction between the halogen derivatives of these and *Grignard* compounds.

$\beta\beta$ -Dialkyl hydroxylamines  $\text{N}(\text{C}_2\text{H}_5)_2\cdot\text{OH}$  are formed by the action of alkyl magnesium bromides on nitro paraffins, on



esters of nitrous acid, and even esters of nitric acid (J. C. S., 1921, 251).

*Grignard* compounds react with the ethyl esters of aliphatic sulphonic acids yielding sulphones (p. 100).



The esters of aromatic sulphonic acid do not react in the same manner (*Ferns and Lapworth*, J. C. S., 1912, 283).

With dibromo derivatives of saturated hydrocarbons magnesium can behave in one of two ways. (a) It can remove the halogen as magnesium bromide yielding an olefine or even a cyclic hydrocarbon, e.g. 1 : 2-dibromoethane yields ethylene and 1 : 3-dibromopropane yields cyclopropane with some propylene (*Grignard*). (b) With compounds such as 1 : 4-dibromobutane, 1 : 5-dibromopentane and 1 : 7-dibromoheptane, a certain amount of the dimagnesium compound  $\text{BrMg}(\text{C}_n\text{H}_{2n})_x\text{MgBr}$  is formed, but there is no formation of cyclic or unsaturated hydrocarbons and no mono magnesium compound of the type  $\text{BrMg}(\text{C}_n\text{H}_{2n})_x\text{Br}$  can be isolated (*Von Braun and Sobiecki*, B., 1911, 1918). A tribromo compound of the type  $\text{CH}_2\text{Br} \cdot \text{CHBr} \cdot (\text{CH}_2)_n \cdot \text{CH}_2\text{Br}$  reacts with magnesium giving an unsaturated *Grignard* reagent, viz.  $\text{CH}_2 : \text{CH}(\text{CH}_2)_n \cdot \text{CH}_2 \cdot \text{MgBr}$  (B., 1919, 1713).

The magnesium compounds of the type  $\text{BrMg} \cdot (\text{CH}_2)_n \cdot \text{MgBr}$  have been used for preparing cyclic compounds containing mercury and other elements as part of the ring (Chap. XXXIX). For the use of *Grignard* compounds in preparation of benzene hydrocarbons see Chap. XVIII, A.; acids, Chap. VI, A., and XXVI, formation 5h; ketones, Chap. V, B.; aldehydes, Chap. XXV, B.; tertiary alcohols, Chap. XXX; sulphinic acids, Chap. XXIII; synthetic terpenes, Chap. LVII, B., II; complex silicon compounds, Chap. L, B. For a summary of recent work on *Grignard* reagents cf. *Hepworth* (J. S. C. I., 1922, T. 7).

A reaction analogous to the *Grignard* reaction and of considerable importance for synthetical purposes is the *Reformatsky* reaction (cf. Chap. XI, B.), in which zinc, an alkyl iodide, (the ester of a brominated acid (B., 1887, 1210; 1895, 2838), or

even a chloro ester if a little copper powder is added to the zinc) react with a ketone. The active reagent is of the type  $\text{Br}\cdot\text{Zn}\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ , analogous to *Grignard* reagent, and the product is a  $\beta$ -hydroxy ester, e.g.  $\text{HO}\cdot\text{CMe}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ .

The unsaturated compound  $\text{CH}_2\text{:AlI}$  from ethylene iodide and Al in the presence of ether forms an additive compound with iodine (C. R., 1922, 174, 112).

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## V. ALDEHYDES AND KETONES, $\text{C}_n\text{H}_{2n}\text{O}$

The aldehydes and ketones are substances which are respectively formed by the oxidation of the primary and secondary alcohols, the oxidation consisting in the elimination of two atoms of hydrogen from each molecule of alcohol.

The aldehydes are formed from the primary alcohols, and are easily converted by further oxidation into the corresponding acids containing an equal number of carbon atoms, oxygen being taken up. They possess in consequence strongly reducing properties.

The ketones result from the oxidation of the secondary alcohols, and are more difficult to oxidize further; they do not possess reducing properties. Their oxidation does not lead to acids containing an equal number of carbon atoms in the molecule, but to others containing a smaller number, the carbon chain being broken.

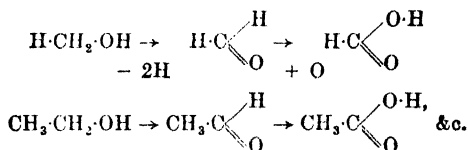
The lower members of both classes are neutral liquids of peculiar smell, readily soluble in water and readily volatile, only  $\text{CH}_2\text{O}$  being gaseous. As the number of carbon atoms increases they become less soluble, and their odour becomes less marked with rise of boiling-point until the highest members are solid, odourless like paraffin, and only capable of being distilled under reduced pressure.

The aldehydes closely resemble the ketones as regards modes of formation and also in many of their properties.

Both groups of compounds contain the carbonyl  $\text{:C:O}$  group, but in the aldehydes this is always attached to a hydrogen atom, and also to an alkyl group or a second hydrogen, e.g.  $\text{CH}_3\cdot\text{CO}\cdot\text{H}$  and  $\text{H}\cdot\text{CO}\cdot\text{H}$ , whereas in a ketone it is attached to two alkyl groups, e.g.  $\text{C}_2\text{H}_5\cdot\text{CO}\cdot\text{C}_2\text{H}_5$ .

## A. Aldehydes

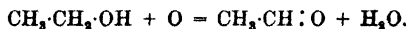
The homologous series of the aldehydes,  $C_nH_{2n}O$ , corresponds exactly with that of the acids,  $C_nH_{2n}O_2$ . They form a group of compounds exactly intermediate between the primary alcohols and the fatty acids. Each primary alcohol by the loss of hydrogen yields an aldehyde, and this by the addition of oxygen yields a fatty acid:



Their boiling-points are decidedly lower than those of the corresponding alcohols, and rise, in the normal aldehydes, at first by about  $27^\circ$  for each  $\text{CH}_2$ , and later on by a less amount.

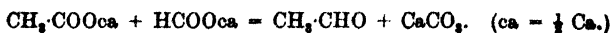
*Nomenclature.*—The name aldehyde is derived from *al*(cohol), *dehyd*(rogenatus), i.e. an alcohol from which hydrogen has been removed. The various aldehydes are named according to the acids to which they give rise on oxidation. For example,  $\text{H}\cdot\text{CHO}$  formaldehyde,  $\text{CH}_3\cdot\text{CHO}$  acetaldehyde, &c. According to the Geneva Congress, the aldehydes receive names ending in *al*, e.g. ethanal for acetaldehyde.

*Modes of Formation.*—1. By the regulated oxidation of the primary alcohols,  $C_nH_{2n+1}\text{OH}$ , by potassium dichromate or manganese dioxide and dilute sulphuric acid, with higher alcohols other products, e.g. acids, and especially esters are also formed; often slowly by atmospheric oxygen, especially in the presence of bone-black or platinum:



The best method is often the catalytic dehydrogenation of the alcohol at  $300^\circ$  (cf. Chap. XLIX, C.).

2. From the acids of the acetic series, by distilling a mixture of their calcium or barium salts with calcium or barium formate (*Limpricht*). The formic acid acts in this instance as a reducing agent, producing calcium carbonate, thus:

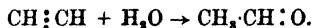


3. From the dihalogen substitution products of the hydrocarbons containing the group  $\cdot\text{CHX}_2$ , by superheating with water or by boiling with water and  $\text{PbO}$ :



4. From *Grignard* reagents (Chap. IV, H.), and ethyl formate or ethyl orthoformate.

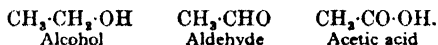
5. An interesting synthesis is from acetylene hydrocarbons by the addition of water under the influence of sulphuric acid and a mercury salt.



(Cf. Chap. LI, F.)

6. An aldehyde can also be formed from a nitrile by the addition of  $\text{HCl}$  to yield the compound  $\text{R}\cdot\text{CCl}:\text{NH}$ , and this on reduction or hydrolysis gives the aldehyde  $\text{R}\cdot\text{CH}:\text{O}$  (J. C. S., 1925, 1874; 1933, 39).

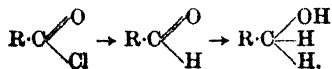
*Constitution.*—In the oxidation of the primary alcohols,  $\text{R}\cdot\text{CH}_2\cdot\text{OH}$ , to their corresponding acids,  $\text{R}\cdot\text{CO}\cdot\text{OH}$ , the alkyl radical  $\text{R}$  remains unaltered. It must consequently also remain unchanged in the intermediate products of the oxidation, viz. the aldehydes, which therefore possess the constitution  $\text{R}\cdot\text{CHO}$ ;



The aldehydes thus contain the group  $\cdot\text{CHO}$ , either  $\cdot\text{C}\cdot\text{OH}$  or  $\cdot\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{H} \end{smallmatrix}$ . The former is improbable, as the aldehydes do not,

as a rule, give reactions characteristic of compounds containing hydroxyl radicals. All their properties point to the presence of the  $\text{:C:O}$  group. The characteristic grouping of all aldehydes is thus the  $\cdot\text{C}\begin{smallmatrix} \text{H} \\ // \\ \text{O} \end{smallmatrix}$  group. This is confirmed by the fact

that an acid chloride  $\text{R}\cdot\text{C}\begin{smallmatrix} \text{O} \\ // \\ \text{Cl} \end{smallmatrix}$  on reduction yields a primary alcohol and in certain cases an aldehyde can be isolated (Chap. VII, B.):



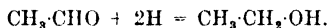
*Isomers.*—Isomerism in the aldehydes is caused solely by isomerism in the alkyl radicals R, which are combined with the group  $\cdot\text{CHO}$ , and therefore contain an atom of carbon less. Otherwise the aldehydes—from  $\text{C}_3\text{H}_6\text{O}$  on—are isomeric with the ketones, with the oxides of the olefines (acetaldehyde with ethylene oxide,  $\text{C}_2\text{H}_4\text{O}$ ), and with the alcohols of the allylic series.

*Behaviour.*—The aldehydes are distinguished by being exceptionally chemically active.

1. The aldehydes are very readily oxidizable, slowly even by the air alone, and quickly by chromic acid, salts of the noble metals, &c. They consequently reduce an ammoniacal solution of silver and often one of copper; this reaction is characteristic and is especially delicate in the presence of caustic-soda solution. (Formation of silver mirror.)

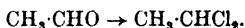
The catalytic oxidation of acetaldehyde to acetic acid both in the gaseous phase at  $150\text{--}200^\circ$  and in the liquid phase at  $0^\circ$  with ferric oxide is used technically.

2. The aldehydes are easily reduced by nascent hydrogen, e.g. sodium amalgam and dilute acid or zinc dust and glacial acetic acid, or best by  $\text{Al}(\text{OEt})_3$  (cf. Ketones), to the primary alcohols from which they are derived by oxidation, e.g.:



A glycol is formed as a by-product, e.g. butylene glycol,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}_3$  from  $\text{CH}_3\cdot\text{CH}:\text{O}$ .

3. Phosphorus pentachloride and trichloride convert the aldehydes into ethylidene chloride and analogous dichloro-substitution products of the hydrocarbons;

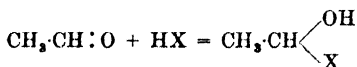


4. Additive reactions. According to *Perkin* (J. C. S., 1887, 808), a solution of acetaldehyde in water contains a certain amount of the hydrate,  $\text{CH}_3\cdot\text{CH}(\text{OH})_2$ . (Cf. Chloral hydrate.) This compound is extremely unstable, and has never been isolated in a pure form. In those reactions in which it might be formed, its anhydride (acetaldehyde) is invariably produced, e.g.  $\text{CH}_3\cdot\text{CHCl}_2$  with alkali yields  $\text{CH}_3\cdot\text{CH}:\text{O}$  as final product, and not  $\text{CH}_3\cdot\text{CH}(\text{OH})_2$ , although this is probably formed as an intermediate.

It follows that a compound with two hydroxyl groups attached to the same carbon atom is usually unstable and tends to lose a

molecule of water yielding an aldehyde or ketone. In particular cases only can compounds with two such hydroxyl groups exist (see Chloral).

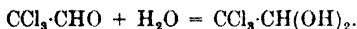
If, in place of water,  $\text{NaHSO}_3$ ,  $\text{NH}_3$ ,  $\text{HCN}$ , &c., be employed, direct addition to the aldehydes is readily observed, and in all these reactions it is concluded that the addition occurs at the expense of the doubly-united oxygen atom. A hydrogen atom of the substance in question attaches itself to the oxygen of the aldehyde, with formation of a hydroxyl group, while the residual X (e.g.  $\text{CN}$ ), which was originally bound to the afore-mentioned H atom, becomes attached to the carbon:



Cf. additive reactions of the olefines (p. 46).

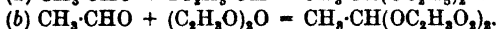
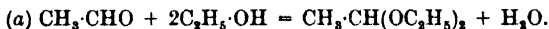
The most important additive reactions are:

(a) Combination with water, which would lead to a dihydric alcohol, does not as a rule take place, for the reasons already given. Should the alkyl radical of the aldehyde, however, contain several negative atoms, e.g. Cl, then the hydrates are capable of existence, for instance chloral hydrate:



But even in these cases the tendency for water to separate is too great to allow of such hydrates behaving as dihydric alcohols; they react rather, for the most part, exactly like the aldehydes themselves. (Cf. Pyroracemic and Mesoxalic acids.)

(b) Occasionally, compounds with alcohol or acetic acid, e.g.  $\text{R}\cdot\text{CH}(\text{OEt})(\text{OH})$ , or  $\text{R}\cdot\text{CH}(\text{OH})(\text{OAc})$ , are met with. They are, however, extremely unstable. When the aldehyde is heated with (a) an alcohol with a little sulphuric acid or ammonium chloride (J. C. S., 1922, 79), or (b) acetic anhydride, stable ethers or esters of the hypothetical glycols are obtained:



The compounds obtained from alcohols, the so-called "**acetals**" (see p. 152), are also formed by the partial oxidation of primary alcohols, and are hydrolysed by sulphuric acid.

Corresponding with the acetals are the **mercaptals** formed by heating an aldehyde with a mercaptan, e.g.:



(c) The aldehydes combine with sodium hydrogen sulphite,  $\text{NaHSO}_3$ , &c., to crystalline compounds, readily soluble in water but sparingly in alcohol, e.g.  $\text{C}_2\text{H}_4\text{O}$ ,  $\text{NaHSO}_3$ ,  $\frac{1}{2}\text{H}_2\text{O}$ . These are to be regarded as sulphite derivatives of the ethylidene glycols, for instance,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot(\text{O}\cdot\text{SO}_2\text{Na})$ . (B., 1928, 179.) They are almost invariably decomposed when heated with alkalis or acids and regenerate the aldehydes, and are of importance for the separation of aldehydes from mixtures.

(d) The aldehydes combine with ammonia to aldehyde-ammonias, e.g. **aldehyde-ammonia**,  $(\text{CH}_3\cdot\text{CHO}, \text{NH}_3)_3$ .\* These are crystalline compounds, for the most part readily soluble in water, sparingly in alcohol, and insoluble in ether. Like the bisulphite compounds, they are advantageously used for the purification of aldehydes, as they readily yield the aldehydes when warmed with dilute acid. (See p. 151.)

(e) The aldehydes combine with hydrocyanic acid to form nitriles of higher acids; thus acetaldehyde yields the com-

pound  $\text{CH}_3\cdot\text{CH}\begin{matrix} \text{OH} \\ \text{CN} \end{matrix}$ , **ethylidene cyanhydrin**. This reaction

is largely made use of in the preparation of certain hydroxy acids, as the cyanhydrins, when hydrolysed, yield hydroxy

acids, e.g.  $\text{CH}_3\cdot\text{CH}\begin{matrix} \text{OH} \\ \text{COOH} \end{matrix}$ , lactic acid.

The action is accelerated by the presence of an alkali or of a metallic cyanide, i.e. of the  $\text{CN}$  ion (cf. *W. J. Jones*, J. C. S., 1914, 1560).

(f) An interesting additive reaction is that between an aldehyde and a *Grignard* compound (p. 141). Thus acetal-

dehyde and magnesium ethyl iodide yield  $\text{CH}_3\begin{matrix} \text{CH}_3 \\ \text{C}_2\text{H}_5 \end{matrix}\text{CH}\cdot\text{OMgI}$ ,

and this with water gives methyl-ethyl-carbinol,  $\text{CH}_3\begin{matrix} \text{CH}_3 \\ \text{C}_2\text{H}_5 \end{matrix}\text{CH}\cdot\text{OH}$ .

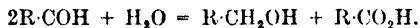
5. The aldehydes show great tendency to polymerize. (See pp. 6 and 48.) In the case of formaldehyde this polymerization occurs spontaneously at the ordinary temperature. Acetaldehyde is polymerized upon the addition of small quan-

\* According to *Aschan* (B., 1915, 874), has ml.-pt. 95-99°, and is  $\text{OH}\cdot\text{CHMe}\cdot\text{NH}_2(\text{OH})\cdot\text{CHMe}\cdot\text{NH}_2(\text{OH})\cdot\text{CHMe}\cdot\text{NH}_2$ .

tities of hydrochloric, sulphuric, or sulphurous acid, zinc chloride, carbonyl chloride, &c., to para-aldehyde,  $C_6H_{12}O_3$ ,  $= (C_2H_4O)_3$ , at the ordinary temperature, and to meta-aldehyde,  $(C_2H_4O)_3$ , at  $0^\circ$ .

Another type of polymerization is the aldol condensation (see below and 154).

6. Aldehyde and several of its homologues, when heated with caustic-soda solution, are transformed into a reddish-brown resin termed **aldehyde-resin**, a product insoluble in water but soluble in alcohol, and possessing a peculiar odour. Many aldehydes are transformed by alkalis into a mixture of equivalent amounts of alcohol and acid, the **Cannizaro** reaction (1853), or dismutation of aldehydes, a reaction given by most aldehydes which do not polymerize to aldols.



When  $Al(OEt)_3$  is used in place of an alkali the product is usually the ester  $R \cdot CO \cdot O \cdot CH_2R$  and not the alcohol and acid.

7. The aldehydes show a great tendency to form *condensation* products with aldehydes, ketones, acids, &c. (See Croton-aldehyde, Cinnamic acid, &c.)

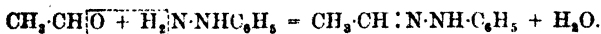


It is probable that in all these condensations direct addition first occurs; for example, in (a) aldol,  $CH_3 \cdot CH(OH) \cdot CH_2 \cdot CHO$ , is first formed, and then by the loss of water forms croton-aldehyde,  $CH_3 \cdot CH : CH \cdot CHO$ . (See p. 154.)

8. With hydroxylamine the aldehydes yield the so-called **Aldoximes**, water being eliminated (*V. Meyer*, B., 1882, 2778; 1890, 2769).



9. The aldehydes react with hydrazines to form the so-called **Hydrazones**, water being eliminated. Phenylhydrazine is the reagent usually employed, but substituted compounds such as *p*-nitro- and 2:4-dinitro-phenylhydrazine are also used.



Aldehyde-phenyl-hydrazone



Most of the phenylhydrazones are somewhat sparingly soluble in alcohol, crystallize very readily, and are made use of in identifying different aldehydes. On reduction they yield primary amines:



10. Moist chlorine and bromine act upon the aldehydes as substituents; thus, from acetaldehyde chloral is obtained:



11. Sulphuretted hydrogen converts the aldehydes into thio-aldehydes. These are compounds of unpleasant aromatic odour, which show the same peculiarities of polymerization as the aldehydes (*Klinger*). (Cf. *E. Baumann*, B., 1890, 60; 1892, 1419, 3591).

Reactions 8 and 9 may also be regarded as condensations. It is possible that in all these reactions direct addition first occurs, and that water is subsequently eliminated.

*Tests for aldehydes:*

(1) Behaviour with ammoniacal silver-nitrate solution (p. 146, and also B., 1882, 1629).

(2) Behaviour with alkaline bisulphites (p. 148).

(3) Behaviour with phenyl-hydrazine and hydroxylamine (see above).

(4) Aldehydes colour a solution of magenta which has been decolorized by sulphurous acid (*Schiff's* reagent) an intense violet-red; some ketones and chloral, but not chloral hydrate, produce the same effect.

**Formaldehyde**, *Methanal*,  $\text{H}\cdot\text{CH}:\text{O}$ , may be regarded as the oxide of the divalent methylene radical,  $\text{CH}_2\cdot$ . An aqueous solution containing methanal is obtained by passing the vapour of methyl alcohol with air over heated copper or platinized asbestos. **Formalin** is the commercial 40 per cent solution obtained by using copper. It is also a product of the action of ozone or of oxygen on methane (B., 1912, 3515; J. S. C. I., 1922, 303T). It can be condensed to a volatile liquid boiling at  $-21^\circ$ . It is largely used as an antiseptic and disinfectant, for hardening organic tissues and gelatin, also for condensing with phenols to yield the product known as **Bakelite**, and is also used as a methylating agent.

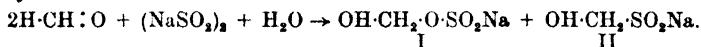
Its chief polymeric forms are:

(1) **Para-formaldehyde**, probably  $(\text{CH}_2\text{O})_n$ , a white mass,

m.-pt.  $160^{\circ}$ , soluble in water; on heating it yields formaldehyde and is used for fumigating rooms in cases of infectious diseases; (2) **trioxy-methylene**, probably  $(\text{CH}_2\text{O})_3$ , a crystalline compound obtained by cooling the gas to below  $-20^{\circ}$ , is insoluble in water, melts at  $171^{\circ}$  and probably has a cyclic structure; it yields formaldehyde when volatilized. (3) **Formose** (Chap. XIV, A.), a mixture of several compounds of the nature of glucose. On account of this facility for undergoing polymerization, formaldehyde in all probability plays an important part in assimilation by plants.

It does not form an additive compound with ammonia, but condenses to the complex compound  $\text{C}_6\text{H}_{12}\text{N}_4$ , hexamethyleneamine, known commercially as hexamine or urotropine and used as a urinary disinfectant. It is also used for estimating ammonium salts.

Formaldehyde reacts with sodium hyposulphite  $\text{NaSO}_2$ , yielding formaldehyde bisulphite (I) and formaldehyde sulphoxylate (II) (**rongalite**), a valuable reducing agent used in dye works:



By its combination with hydrochloric acid, **chloro-methyl alcohol** (*chloro-methanol*),  $\text{CH}_2\text{Cl}(\text{OH})$ , and **hydroxy-chloro-methyl ether** (*chloromethane-oxy-methanol*),  $\text{CH}_2\text{Cl}\cdot\text{O}\cdot\text{CH}_2\text{OH}$ , are formed. Both of these are colourless liquids, which react in many respects like formaldehyde itself.

**Methylal**,  $\text{CH}_2(\text{OCH}_3)_2$ , (see Acetals, p. 147), is frequently made use of, instead of formaldehyde, for carrying out condensation reactions. It is employed in medicine as a soporific, and is also used as an extractive for certain scents. B.-pt.  $42^{\circ}$ .

**Acetaldehyde**, *Ethanal*, *Aldehyde*,  $\text{CH}_3\cdot\text{CHO}$ , was formerly termed "acetyl hydride",  $\text{C}_2\text{H}_3\text{O}\cdot\text{H}$  (*Fourcroy* and *Vauquelin*, 1890; composition established by *Liebig* in 1835). It is prepared by passing ammonia gas into an ethereal solution of the crude aldehyde, obtained by oxidizing alcohol with  $\text{K}_2\text{Cr}_2\text{O}_7$  +  $\text{H}_2\text{SO}_4$  and drying over  $\text{CaCl}_2$ , washing the precipitated aldehyde-ammonia with ether, and finally distilling it with dilute sulphuric acid. It is obtained in large quantity as a by-product in the first portions of the distillate "**First Runnings**" in the manufacture of spirit. For its production in place of vinyl alcohol,  $\text{CH}_2:\text{CH}\cdot\text{OH}$ , from acetylene, see pp. 54 and 91.

It is produced commercially (a) by the addition of water to

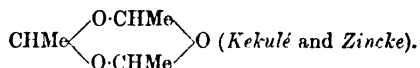
acetylene under the influence of mercury and its salts (p. 54 and Chap. LI, F.); (b) by dehydrogenation of alcohol vapour by passing over heated copper at  $280^\circ$ , after each passage about 20–25 per cent of the alcohol is dehydrogenated; (c) by oxidizing alcohol vapour with atmospheric oxygen and a silver catalyst. As the reaction is endothermic no cooling is required and the yield is good.

It is a colourless mobile liquid, boils at  $21^\circ$ , and has sp. gr. about 0.8. Its odour is aromatic and suffocating, and produces a kind of cramp in the chest when inhaled. It burns with a luminous flame, dissolves sulphur, phosphorus, and iodine, and is readily soluble in water, alcohol, and ether.

**Para-aldehyde**,  $C_6H_{12}O_3$ , is a liquid sparingly soluble in water. It melts at  $10^\circ$ , and boils at  $124^\circ$ , i.e. more than  $100^\circ$  above aldehyde, and is used as a soporific.

**Meta-aldehyde**,  $(C_2H_4O)_x$ , crystallizes in white prisms insoluble in water, and sublimes at a little over  $100^\circ$ , but is partially reconverted into aldehyde. It is inflammable and used as a solid fuel (metol).

Meta-aldehyde is changed back again into ordinary aldehyde by prolonged heating to  $115^\circ$  in sealed tubes, and also, as is the case with para-aldehyde, by distillation with somewhat dilute sulphuric acid. Para-aldehyde reacts in the same way as ordinary aldehyde with  $PCl_5$ , but not with  $NH_3$ ,  $NaHSO_3$ ,  $AgNO_3$ , and  $NH_2OH$ . This constitution of para-aldehyde may be represented as:



A study of these and other polymeric compounds shows that with substances of similar structure the one of simpler composition is the more soluble, possesses the lower melting-point, and is the more easily vaporized.

**Acetal**,  $CH_3 \cdot CH(OC_2H_5)_2$ , boils at  $104^\circ$ . It is usually obtained by the partial oxidation of ethyl alcohol with manganese dioxide and sulphuric acid, the acetaldehyde first formed condensing with the alcohol with the production of acetal. This, as well as methylal, is frequently used instead of aldehyde for the carrying out of condensation reactions (see p. 149), and like para-aldehyde is used as a diluent in the nitro-cellulose industry.

**Propaldehyde**,  $C_2H_5 \cdot CHO$ , is present in wood-tar. *n*-Butaldehyde is a commercial product used in the rubber industry and can be obtained by the catalytic hydrogenation of crotonaldehyde or passing *n*-butyl alcohol vapour over heated  $CuO$ , b.-pt.  $73^\circ$ . *n*-heptaldehyde (*ænanthal*),  $C_7H_{14}O$ , is obtained by the dry distillation of castor-oil under diminished pressure.

**Chloral**, 2-trichloro-ethanal,  $CCl_3 \cdot CHO$ , is a liquid which boils at  $98^\circ$ , and which—when impure—easily changes into a solid polymeric modification, meta-chloral, but is regenerated from this upon heating. It combines readily with water to **chloral hydrate**,  $CCl_3 \cdot CH(OH)_2$  (see p. 147, *a*), and with alcohol to **chloral alcoholate**,  $CCl_3 \cdot CH(OH)(OC_2H_5)$ , and **tri-chloro-acetal**,  $CCl_3 \cdot CH(O \cdot C_2H_5)_2$ . The end product of the action of chlorine upon alcohol consists chiefly of the last three substances. They are all colourless crystalline compounds, which are converted into chloral by distilling with sulphuric acid, and rectifying over lime.

Chloral is an oily liquid with a sharp, characteristic odour. It combines with sodium bisulphite, ammonia, hydrocyanic acid, and acetic anhydride, and reduces an ammoniacal solution of silver oxide. It is readily oxidized to trichloroacetic acid, and decomposed by alkali into chloroform and an alkali formate (cf. p. 68).

For properties of aldehydes and their derivatives, cf. *Harries*, C. Z., 1916, ii, 991.

**Chloral hydrate**,  $CCl_3 \cdot CH(OH)_2$ , forms large colourless crystals readily soluble in water, melting at  $57^\circ$ , and boiling with dissociation at  $97^\circ$ . It acts as a soporific and antiseptic. Sulphuric acid converts it into chloral.

## UNSATURATED ALDEHYDES

**Acrolein**, *Acr-aldehyde*, *propenal*,  $CH_2 : CH \cdot CHO$ , is formed by the oxidation of allyl alcohol, by the distillation of fats, and by heating glycerol with anhydrous magnesium sulphate (B., 1912, 204). It is a liquid boiling at  $52^\circ$ , of pungent odour (the smell of burning fat being due to it), and of violent action upon the mucous membrane of the eyes. It unites in itself the properties of an aldehyde and of an unsaturated carbon compound, and therefore combines with ammonia and with bromine; it also unites with hydrogen bromide to *bromopropylaldehyde*,  $CH_2Br \cdot CH_2 \cdot CHO$ .

When distilled, acrolein-ammonia yields picoline,  $C_6H_7N$  (see Pyridine bases); and crotonaldehyde-ammonia, by an analogous reaction, collidine,  $C_8H_{11}N$ .

Acrolein can combine with two atoms of bromine to acrolein dibromide (dibromoprop-aldehyde),  $CH_2Br\cdot CHBr\cdot CHO$ , a compound which is of importance in the synthesis of the sugars. (See Synthesis of Hexoses. Chap. XIV, A.)

**Croton-aldehyde**,  $CH_3\cdot CH:CH\cdot CHO$ . When acetaldehyde is left for some time in contact with dilute hydrochloric acid or sodium hydroxide, polymerization occurs, and a substance termed **aldol**,  $\beta$ - or 3-hydroxy-butylaldehyde, is obtained,  $CH_3\cdot CH(OH)\cdot CH_2\cdot CHO$ . The constitution of aldol follows from its properties. It cannot be readily converted back into acetaldehyde, and in this respect differs from the other polymeric forms, viz. meta- and para-aldehyde. This difference is due to the fact that in the aldol condensation the union of the molecules has been brought about between carbon atoms, and hence the relative stability. Aldol when distilled or in presence of dehydrating agents yields croton-aldehyde, water being eliminated.



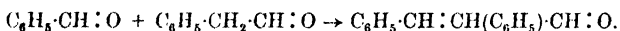
Aldol is an important intermediate in the manufacture of *n*-butyl alcohol from acetaldehyde. The polymerization to aldol is accomplished by alkaline catalysts (1 per cent  $Na_2CO_3$ ), and must be carried out in a non-oxidizing atmosphere and with careful temperature control as the reaction is exothermic and may become explosive. The dehydration of the aldol to crotonaldehyde requires careful regulation of  $p_H$  in order to avoid formation of resins and the crotonaldehyde is immediately removed by excess steam. The last stage viz. the reduction of crotonaldehyde to *n*-butyl alcohol is by hydrogenation in either liquid or vapour phase with a nickel catalyst.

The last two stages may be combined by hydrogenating the aldol with a nickel chromite catalyst under pressure. Reduction to 1:3-butylene glycol,  $OH\cdot CH_2\cdot CH_2\cdot CH(OH)\cdot CH_3$ , may occur but this becomes dehydrated to crotonyl alcohol,  $OH\cdot CH_2\cdot CH:CH\cdot CH_3$ , which yields *n*-butyl alcohol.

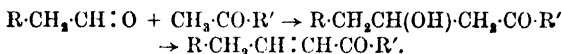
The aldol condensation is characteristic of aldehydes with the grouping  $R\cdot CH_2\cdot CHO$



the product being a  $\beta$ -hydroxyaldehyde. The usual condensing agents are  $K_2CO_3$ , KCN,  $NaO\cdot Ac$ , dil NaOH. If  $ZnCl_2$  is used the product is usually the unsaturated aldehyde corresponding with crotonaldehyde. The two aldehyde molecules may be different, e.g. benzaldehyde and phenylacetaldehyde:



Similarly, certain ketones can react with an aldehyde  $R\cdot CH_2\cdot CHO$ , giving a hydroxyketone or by loss of water an unsaturated ketone



(*Morgan and Hardy*, C. I., 1933, 518.)

## B. Ketones

The lowest member of the series, Acetone, contains three atoms of carbon. The higher members, from  $C_{12}$  on, are solid. They are all lighter than water; e.g. the sp. gr. of acetone is 0.81 at  $0^\circ$ .

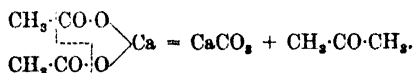
*Occurrence.*—Acetone is present in urine, methyl-nonyl ketone in oil of rue, and also with homologues in cocoanut oil.

*Modes of Formation.*—1. By the oxidation of secondary alcohols; just as in the conversion of a primary alcohol to an aldehyde, this oxidation consists in the withdrawal of two hydrogen atoms from each molecule of the alcohol:



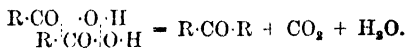
Many primary and secondary alcohols are decomposed into hydrogen and aldehyde (or ketone) when heated in contact with a catalyst (see Chap. XLIX, C.).

2. By the dry distillation of the calcium or barium salts of fatty acids at about  $400^\circ$ :



Some of the ketones of high molecular weight may be obtained by heating fatty acids with phosphorus pentoxide

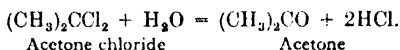
(Kipping), or even heating the acids at 295° for three hours:



When a mixture of two calcium salts is taken a **mixed ketone** is formed; thus calcium acetate and calcium propionate yield methyl ethyl ketone. As a rule, in addition to the mixed ketone, the two simple ketones, e.g.  $(\text{CH}_3)_2\text{CO}$  and  $(\text{C}_2\text{H}_5)_2\text{CO}$ , are also formed.

A modification of this method is to pass the vapour of the acid over heated carbonate of calcium, barium, or manganese (cf. Chap. XLIX, F.).

3. From dichlorides containing the group  $\text{C} \cdot \text{CCl}_2 \cdot \text{C}$ :



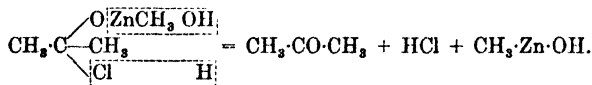
It is probable that the chlorine atoms are first replaced by hydroxyls, yielding the glycol,  $\text{CMe}_2(\text{OH})_2$ , which immediately eliminates  $\text{H}_2\text{O}$ , yielding the ketone,  $\text{CMe}_2\text{O}$ .

4. By methylating an aldehyde with diazo-methane,  $\text{CH}_2\text{N}_2$  (B., 1907, 479; 1909, 2561), but a compound  $\begin{array}{c} \text{R} \cdot \text{CH} \\ | \\ \text{CH}_2 \end{array} \text{O}$  is also formed (B., 1928, 1110).

5. By the action of zinc alkyl upon an acid chloride, e.g. acetyl chloride,  $\text{CH}_3 \cdot \text{COCl}$ .

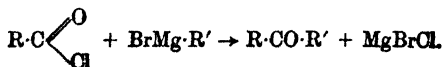
An additive compound is first formed,  $\text{CH}_3 \cdot \text{C} \begin{array}{l} \nearrow \text{OZnCH}_3 \\ \searrow \text{CH}_3 \\ \text{Cl} \end{array}$ ,

which must be quickly decomposed by water, otherwise tertiary alcohols are produced:

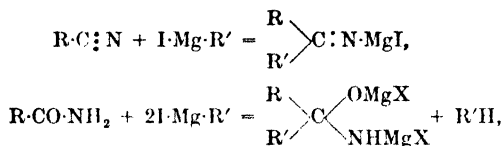


This method of formation, which was devised by *Freund* in 1861, allows of the preparation of any possible ketone by using the requisite zinc alkyl and acid chloride.

An analogous reaction is that of an acid chloride with a *Grignard* reagent:



Ketones have been synthesized by the action of organo-magnesium compounds on nitriles or acid amides, e.g.:



and these with water yield  $\text{R}\cdot\text{CO}\cdot\text{R}'$ . (*Blaise, C.*, 1901, **132**, 38, **133**, 299; *Bull. Soc. Bel.* 1922, 184, 231.)

Methods 2 and 5 elucidate the *constitution* of the ketones from the constitution of the corresponding acids. Conclusions regarding constitution based on the former method (No. 2) must be accepted with a considerable amount of reserve unless supported by other arguments, since in reactions which occur at high temperatures intramolecular rearrangements can readily occur. Theoretically, therefore, ketones are compounds which contain the carbonyl group, CO, linked on both sides with an alkyl radical,  $\text{R}\cdot\text{CO}\cdot\text{R}$ . If the alcohol radicals are the same, "**simple**" ketones result; and if different, "**mixed**" ketones. A compound with less than 3 C atoms is thus impossible.

6. From the ketonic acids or their esters, e.g. acetoacetic ester,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , by warming with moderately dilute sulphuric acid or with dilute alkalis. This important reaction will be treated of at greater length under acetoacetic ester (Chap. IX, H.).

7. By the addition of water to homologues of acetylene,  $\text{CH}_3\cdot\text{C}\text{:}\text{CH} + \text{H}_2\text{O} = \text{CH}_3\cdot\text{CO}\cdot\text{CH}_3$ . This reaction occurs at relatively high temperatures, or may be brought about indirectly by the aid of sulphuric acid, or solutions of mercuric salts (cf. Acetylenes, Chap. I, C., and LI, F.).

8. Some of the higher ketones can be synthesized from a simpler ketone and an alcohol by passing the vapour diluted with  $\text{N}_2$  over a suitable catalyst, e.g. aluminium-copper oxide activated by Mo or Ag at  $230^\circ$  and 30 atm., e.g. acetone and *n*-butyl alcohol yield methyl amyl ketone.

*Isomers.*—The ketones exhibit (a) metamerism, i.e. isomerism within the alkyl group; cf. *n*-propyl and *iso*-propyl ketones. (b) Position isomerism due to the position of the CO group; cf. methyl propyl ketone and diethyl ketone. (c) Isomerism



with the aldehydes; cf. propaldehyde and acetone. (*d*) Saturation isomerism, cf. acetone and allyl alcohol:  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_3$  and  $\text{CH}_2\text{:CH}\cdot\text{CH}_2\cdot\text{OH}$ .

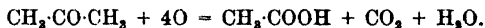
*Nomenclature*.—The usual name is formed by adding the suffix ketone to the name of the alkyl groups present; e.g.  $(\text{C}_2\text{H}_5)_2\text{CO}$ , diethyl ketone;  $\text{CH}_3\cdot\text{CO}\cdot\text{C}_2\text{H}_5$ , methyl ethyl ketone, &c. The names of the simple ketones are also derived from the acids which yield them, e.g. "Valerone"  $(\text{C}_4\text{H}_9)_2\text{CO}$ , from valeric acid.

The systematic names of the ketones are formed by taking the name for the corresponding hydrocarbon, adding the syllable one to indicate the O replacing 2H, and then a number to indicate the position of the O atom, e.g.  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_3$ , **butan-2-one**, &c.

*Behaviour*.—1. Reagents which give rise to nascent hydrogen reduce the ketones to secondary alcohols:  $(\text{CH}_3)_2\text{CO} + 2\text{H} = (\text{CH}_3)_2\text{CH}\cdot\text{OH}$ . Small amounts of pinacones (Chap. VIII, A.) are formed at the same time. The usual reducing agents are sodium or sodium amalgam and alcohol or sodium and moist ether or, best, aluminium ethoxide,  $\text{Al}(\text{OEt})_3$ . The method is of general application and can be used for aldehydes, unsaturated aldehydes, ketones and halogenated ketones. A similar reduction occurs when the ketone is heated with hydrazine at  $200^\circ$  (B., 1911, 2206).

Drastic reducing agents, such as amalgamated zinc and concentrated hydrochloric acid, reduce both aldehydes and ketones to the saturated hydrocarbons (Clemmensen, B., 1913, 1837; 1914, 51, 681), a reaction of considerable importance and of general application.

2. Oxidizing agents, e.g.  $\text{K}_2\text{Cr}_2\text{O}_7$ , and dilute  $\text{H}_2\text{SO}_4$ , produce a scission of the chain and a mixture of acids and ketones with a smaller number of carbon atoms in the molecule; cf. Aldehydes, p. 145.



Oxidation analogous to that of the aldehydes is clearly impossible. Oxidation to a ketonic acid is theoretically possible with certain ketones, e.g.  $\text{R}\cdot\text{CO}\cdot\text{CH}_3 \rightarrow \text{R}\cdot\text{CO}\cdot\text{CO}_2\text{H}$ , but occurs only rarely. The scission of the molecule occurs in such a manner that in a mixed ketone the CO group remains attached to the smaller alkyl group. Thus  $\text{CH}_3\cdot\text{CO}\cdot\text{C}_3\text{H}_7$ , on oxidation yields mainly acetic  $\text{CH}_3\cdot\text{CO}_2\text{H}$  and propionic

$C_2H_5\cdot CO_2H$  acids; but at the same time a small amount is oxidized to a mixture of carbonic and butyric acids.

The ketones do not possess reducing properties.

3. Phosphorus pentachloride,  $PCl_5$ , converts the ketones into the corresponding dichlorides, acetone, for instance, into acetone chloride,  $(CH_3)_2CCl_2$ .

4. Additive reactions. (a) The ketones do not as a rule combine with water and alcohol, for the reasons given under the aldehydes.

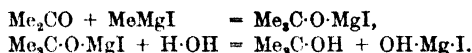
(b) With ammonia they yield complex condensation products, e.g. di-acetone-amine,  $C_8H_{13}NO$ , tri-acetone-amine,  $C_9H_{17}NO$  (*Heintz*); this reaction is more complicated than that with the aldehydes, 2 or 3 molecules of acetone combining with 1 molecule of ammonia, with elimination of water.

(c) The ketones which contain the group  $CH_3\cdot CO\cdot$ , and a few other relatively simple ketones, combine with sodium hydrogen sulphite to crystalline compounds, e.g. acetone to  $(Me_2(OH)\cdot O\cdot SO_2Na, H_2O$ , which yields the ketone when distilled with sodium-carbonate solution. This very important reaction is made use of in separating and purifying the ketones. *Stewart* has (*J. C. S.*, 1905, 185) studied the comparative rates at which some of these compounds are formed.

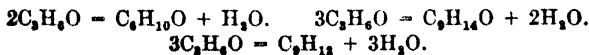
(d) With hydrocyanic acid they yield hydroxy-nitriles, as in the case of the aldehydes; e.g.  $CMe(OH)CN$ .

For acetone cyanhydrin, see *Clems*, *J. C. S.*, 1928, 2629, and for general preparation *Ultee*, *Rec.*, 1909, 248, 257. By using ammonium cyanide an amino-nitrile is formed,  $RR'C(NH_2)CN$ , which are of value as they yield amino-acids on hydrolysis.

(e) Ketones readily form additive compounds with *Grignard's* reagents, and when decomposed with water these yield tertiary alcohols (see p. 80):



5. The ketones, unlike the aldehydes, do not yield polymers, but like formalin form condensation products. Just as aldehyde is converted into crotonaldehyde, so is acetone, by the action of many reagents—e.g.  $CaO$ ,  $KOH$ ,  $HCl$ , and  $H_2SO_4$ —converted, with elimination of water, into **mesityl oxide**,  $C_6H_{10}O$ , **phorone**,  $C_9H_{14}O$ , or **mesitylene**,  $C_9H_{12}$ , according to the conditions (see these substances):



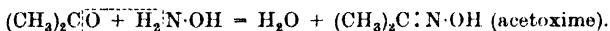
Analogous condensations also ensue with other ketones or aldehydes under the influence of dilute sodium ethoxide.

6. Ketones like aldehydes form acetals  $\text{CMe}_2(\text{OEt})_2$ .

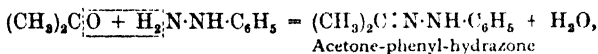
7. Sulphuretted hydrogen converts the ketones into thio-compounds, e.g. acetone into thio-acetone,  $\text{CH}_3\cdot\text{CS}\cdot\text{CH}_3$  (B., 1883, 1368), or their polymers.

8. Halogens give rise to substitution products.

9. Like the aldehydes, the ketones—even  $\text{C}_{35}$ —react with hydroxylamine, yielding oximes, which are termed **Ketoximes** (V. Meyer, B., 1882, 1324, 2778; 1883, 823, 1784, &c.):



10. They react in an analogous manner with phenyl-hydrazine,  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{NH}_2$  (E. Fischer, B., 1884, 572), with the formation of **phenyl-hydrazone** (p. 149).



and with semicarbazide,  $\text{NH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{NH}_2$ , or its hydrochloride yielding **semicarbazones**, e.g.  $(\text{CH}_3)_2\text{C}:\text{N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$ , which crystallize well and have definite melting-points. **Acetaldehyde-semicarbazone** melts at  $162^\circ$ , and **acetone-semicarbazone** at  $189^\circ$ . The three reagents, hydroxylamine, phenyl-hydrazine, and semicarbazide, are extremely useful in detecting and identifying aldehydes and ketones.

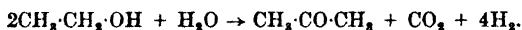
11. Nitrous acid (ethyl nitrite and sodium ethoxide) gives rise to **iso-nitroso-ketones**, e.g. iso-nitroso-acetone,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}:\text{N}\cdot\text{OH}$ , by replacement of  $\text{H}_2$  by the group  $:\text{N}\cdot\text{OH}$  (oximino). When hydrolysed, the  $:\text{N}\cdot\text{OH}$  group is replaced by oxygen, and diketones or aldehydo-ketones are formed.

12. Tertiary ketones,  $\text{CMe}_3\cdot\text{CO}\cdot\text{CMe}_3$  or  $\text{Ph}\cdot\text{CO}\cdot\text{CMe}_3$ , undergo fission with sodamide; the former gives trimethylmethane  $\text{CHMe}_3$  and  $\text{CMe}_3\cdot\text{CO}\cdot\text{NH}_2$  and the latter benzene and the same amide (C. R., 1909, 148, 127; 149, 5).

13. A useful reagent for isolating ketones and separating them from aldehydes is trimethylamino-acetohydrazide (betainehydrazide), as, although it forms condensation products with both aldehydes and ketones, those from the former are stable towards mineral acids; those derived from ketones are readily hydrolysed.

**Acetone**, 2-Propanone,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_3$ . The formula was established by Liebig and Dumas in 1832. It is present in

very small quantity in normal urine, in the blood, in serum, &c., but in much larger quantity in pathological cases such as acetonuria and diabetes mellitus. It is a product of decomposition of cellulose, and is found in wood spirit. It is usually manufactured (a) from calcium acetate made from pyroligneous acid (p. 175); (b) by the fermentation of starch, e.g. maize, by a particular species of bacterium, which yields *n*-butyl alcohol and acetone (J. S. C. I., 1919, 273T: cf. Chap. LXIX, B.). (c) by catalytic oxidation of isopropyl alcohol from the propene of natural or cracked gases. Yield 75 per cent, using ZnO at 320° or Cu at 475–500°; (d) by passing alcohol vapour and steam over rusty iron at 500°:



Even better yields are obtained by using a mixture of alcohol, steam and acetylene.

It is a liquid of peculiar pungent odour; boils at 57·5°, and has sp. gr. 0·81 at 0°. It is soluble in water, but may be salted out from its aqueous solution, and it is also miscible with alcohol and ether.  $\text{KMnO}_4$  does not oxidize it in the cold, but  $\text{CrO}_3$  converts it into acetic and carbonic acids.

It forms a well-defined compound,  $\text{NaI}$ ,  $3\text{C}_3\text{H}_6\text{O}$ , which can be used for purifying it on the laboratory scale (J. C. S., 1913, 1255). With sodium or sodamide it forms the derivative  $\text{CH}_3\cdot\text{C}(\text{ONa})\cdot\text{CH}_3$ , and the higher ketones can be obtained by the action of sodamide and alkyl iodides on acetone or other ketones; thus diethyl ketone, sodamide, and methyl-iodide yield di-isopropyl ketone,  $\text{CHMe}_2\cdot\text{CO}\cdot\text{CHMe}_2$  (Ann. Chim., 1913 [viii], 29, 213). Acetone may be detected by the formation of indigo when its solution in sodium hydroxide is warmed with *o*-nitro-benzaldehyde.

**Sulphonal**,  $\text{CMe}_2(\text{SO}_2\text{Et})_2$ , is formed when a mixture of acetone and mercaptan is treated with hydrochloric acid, and the **mercaptal**,  $(\text{CH}_3)_2\text{C}(\text{SC}_2\text{H}_5)_2$ , which is thus formed, is oxidized by potassium permanganate to the corresponding sulphone. It crystallizes in prisms, melts at 125°, and acts as a soporific.

**Mesityl oxide**,  $(\text{C}_6\text{H}_{10}\text{O})$ , =  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}:\text{C}(\text{CH}_3)_2$  (Kane, 1838; Baeyer), is a liquid of aromatic odour, boiling at 132°.

**Phorone**,  $\text{C}_9\text{H}_{14}\text{O}$ , =  $(\text{CH}_3)_2\text{C}:\text{CH}\cdot\text{CO}\cdot\text{CH}:\text{C}(\text{CH}_3)_2$ , forms readily fusible yellow crystals. Both compounds are obtained by saturating acetone with hydrochloric acid gas (A., 180, 1.)

**Methyl ethyl ketone** (2-*Butanone*),  $\text{CH}_3\cdot\text{CO}\cdot\text{C}_2\text{H}_5$ , is present in crude wood spirit, and is also formed by the oxidation of secondary butyl alcohol. B.-pt.  $81^\circ$ , and is of importance for manufacturing synthetic plastics.

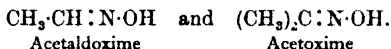
**Pinacoline** (2-*Dimethyl-3-butanone*), *methyl tertiary-butyl ketone*,  $\text{CH}_3\cdot\text{CO}\cdot\text{C}(\text{CH}_3)_3$ , b.-pt.  $106^\circ$ , is produced by the action of dilute sulphuric acid upon pinacone (p. 222). This involves a characteristic rearrangement, the "pinacoline reaction".

A number of ketones have been obtained from the higher fatty acids. These have been converted by *Krafft* into the corresponding paraffins, by first transforming them into the chlorides,  $\text{C}_n\text{H}_{2n}\text{Cl}_2$ , by means of  $\text{PCl}_5$ , and then heating the latter with hydriodic acid and phosphorus.

Both aldehydes and ketones change to the isomeric unsaturated alcohols in presence of hydrogen halides, halogen and *Grignard* reagents; cf. Enolisation, Chap. LIII, A.

## C. Aldoximes and Ketoximes

The aldoximes and ketoximes are the compounds obtained by the action of hydroxylamine on the aldehydes and ketones respectively. They both contain the bivalent oximino group :N·OH attached to carbon, e.g.:



They are either colourless crystalline compounds or liquids, and are both basic and acidic in properties. With metallic hydroxides they yield salts of the type  $\text{CH}_3\cdot\text{CH}:\text{NOK}$ ; with mineral acids they form salts in much the same manner as ammonia does, e.g.  $\text{CMe}_2:\text{NOH}$ ,  $\text{HCl}$ .

The oximes are fairly readily hydrolysed by dilute acids, yielding hydroxylamine and either an aldehyde or a ketone.

On reduction they all yield primary amines, :N·OH  $\rightarrow$  ·NH<sub>2</sub>.

Dehydrating agents, e.g. acetic anhydride or acetyl chloride, transform the aldoximes into nitriles, water being eliminated:



The ketoximes with acetyl chloride followed by water undergo the *Beckmann transformation*, the final product being an acid amide or anilide. Cf. Chap. L, Cl.

*Constitution.*—In the formation of the oximes the water eliminated is undoubtedly formed from the oxygen of the carbonyl group and the hydrogen atoms of the hydroxylamine, otherwise the reaction would be of the type



and an aminoketone would result. There are two possible ways in which water can be thus eliminated, yielding a com-

pound  $\text{CMe}_2\text{:N}\cdot\text{OH}$  or  $\text{CMe}_2\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ | \\ \text{NH} \end{array}$ . That the first of these

two formulæ is correct is demonstrated by the fact that when

an alkyl derivative,  $\text{:C:N}\cdot\text{OR}$  or  $\text{:C}\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ | \\ \text{N}\cdot\text{R} \end{array}$ , is hydrolysed

with hydrochloric acid an alkyl derivative of hydroxylamine,  $\text{NH}_2\cdot\text{OR}$ , is obtained, and hence the alkyl group is presumably attached to oxygen in the alkylated oxime, and the oxime itself thus contains an OH group. This constitution formula is in perfect harmony with the reactions characteristic of oximes.

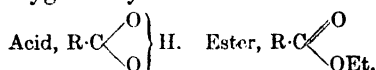
The oxime derived from an aldehyde or ketone often exists in isomeric forms. This is especially true of those derived from aromatic aldehydes and from mixed (unsymmetrical) ketones of the aromatic series. According to *Goldschmidt* and *V. Meyer*, these isomers are structurally identical, and are **stereo-isomeric** (i.e. the isomerism is due to the **spatial relationship** of the various atoms and radicals). See Chap. L, Cl.

## VI. MONOBASIC FATTY ACIDS

### A. Saturated Acids, $\text{C}_n\text{H}_{2n}\text{O}_2$ , or $\text{C}_n\text{H}_{2n+1}\cdot\text{CO}_2\text{H}$

The monobasic fatty acids are formed by the oxidation of the saturated primary alcohols or of their corresponding aldehydes. These acids are monobasic, i.e. contain in the molecule only one replaceable atom of hydrogen, since, as a rule, they give rise to only one series of salts or of esters. They are known as the **fatty acids**, because many of them are contained in fats in the form of glyceryl esters.

The group characteristic of acids is the carboxylic group  $\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \diagup \quad \diagdown \\ \cdot \quad \text{O} \cdot \text{H} \end{array}$ , and it is the hydrogen of this group which becomes replaced in the formation of salts. The basicity of an acid depends on the number of such carboxylic groups present in the molecule. *Hantzsch* (B., 1917, 1422), in order to account for the different absorption spectra given by acids and their esters, suggests that in the acids and their salts the hydrogen or metal is attached to both oxygen atoms (Hydrogen bridge, Chap. XLVI, C), but that in the esters the alkyl group is united to one oxygen only:



Cf. also Resonance, Chap. LXXIII. With the anion  $\text{R} \cdot \text{CO} \cdot \bar{\text{O}}$  the resonance would be  $\text{R}-\text{C} \begin{array}{c} \text{O} \\ \parallel \\ \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array}$  and  $\text{R}-\text{C} \begin{array}{c} \text{O} \\ \parallel \\ \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array}$

#### NORMAL FATTY ACIDS AND THEIR PHYSICAL DATA

				Melting-pt.	Boiling-pt.
Formic acid	..	..	$\text{CH}_2\text{O}_2$	8.3°	101°
Acetic acid	..	..	$\text{C}_2\text{H}_4\text{O}_2$	17	118
Propionic acid	..	..	$\text{C}_3\text{H}_6\text{O}_2$	-22	141
Butyric acid	..	..	$\text{C}_4\text{H}_8\text{O}_2$	-8	164
Valeric acid	..	..	$\text{C}_5\text{H}_{10}\text{O}_2$	-59	186
Caproic acid	..	..	$\text{C}_6\text{H}_{12}\text{O}_2$	+8	205
Heptolic acid	..	..	$\text{C}_7\text{H}_{14}\text{O}_2$	-10	224
Caprylic acid	..	..	$\text{C}_8\text{H}_{16}\text{O}_2$	+16	236
Nonylic acid	..	..	$\text{C}_9\text{H}_{18}\text{O}_2$	12	254
Capric acid	..	..	$\text{C}_{10}\text{H}_{20}\text{O}_2$	31	269
Undecylic acid	..	..	$\text{C}_{11}\text{H}_{22}\text{O}_2$	29	{213
Lauric acid	..	..	$\text{C}_{12}\text{H}_{24}\text{O}_2$	48	{226
Tridecyllic acid	..	..	$\text{C}_{13}\text{H}_{26}\text{O}_2$	51	{236
Myristic acid	..	..	$\text{C}_{14}\text{H}_{28}\text{O}_2$	58	{248
Pentadecylic acid	..	..	$\text{C}_{15}\text{H}_{30}\text{O}_2$	54	{257
Palmitic acid	..	..	$\text{C}_{16}\text{H}_{32}\text{O}_2$	64	{260
Margaric acid	..	..	$\text{C}_{17}\text{H}_{34}\text{O}_2$	60	{277
Stearic acid	..	..	$\text{C}_{18}\text{H}_{36}\text{O}_2$	69	{287
Nondecyllic acid	..	..	$\text{C}_{19}\text{H}_{38}\text{O}_2$	66	{298
Arachidic acid	..	..	$\text{C}_{20}\text{H}_{40}\text{O}_2$	75	—
Behenic acid	..	..	$\text{C}_{22}\text{H}_{44}\text{O}_2$	83	—
Lignoceric acid	..	..	$\text{C}_{24}\text{H}_{48}\text{O}_2$	80	—

The higher acids *Cerotic*,  $C_{26}$ , and *Melissic*,  $C_{30}$ , are probably mixtures.

In numbering the carbon chain the C of the  $CO_2H$  groups is always No. 1, the next C is No. 2, or often called the  $\alpha$  carbon atom, then follows No. 3, or the  $\beta$ , then No. 4, or  $\gamma$ , and so on.

The lower members of the series are liquids of pungent odour and corrosive action, and boil without decomposition. They dissolve readily in water, and the aqueous solutions exhibit a strongly acid reaction, although most of the anhydrous acids are without action on dry litmus paper. The intermediate members have an unpleasant smell like that of rancid butter or perspiration, and are oily and but slightly soluble in water. They ionize in aqueous solution but with the exception of formic acid are weak acids. Mobility, odour, and solubility diminish as the percentage of carbon increases. The higher members, from  $C_{10}$ , are solids, like paraffin, insoluble in water, and can only be distilled without decomposition in a vacuum. These higher acids are readily soluble in alcohol, and especially in ether.

In this series the boiling-point rises regularly for each increase in the number of C atoms in the molecule. The rise is roughly  $19^\circ$  for each increment of  $CH_2$ . The melting-points do not exhibit the same regularity: the melting-point of any acid containing an even number of C atoms in the molecule is higher than the melting-point of the acid with an odd number of C atoms which immediately succeeds it. (Cf. Chap. LXXI, B.)

The specific gravity of the liquid acids is at first  $> 1$ , and from  $C_3$  onwards  $< 1$ , and it decreases continuously to about 0.8, the paraffin character of the hydrocarbon radical becoming preponderant.

*Occurrence.*—Many of the free acids occur in nature, but more frequently as esters, viz.: (a) esters of monohydric alcohols (see wax varieties), (b) esters of glycerol, i.e. glycerides, in most of the vegetable and animal fats and oils. For further particulars see p. 183 and Chap. LV.

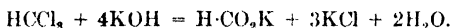
*Formation.*—1. By the oxidation of the primary alcohols,  $R \cdot CH_2 \cdot OH$ , or their aldehydes,  $R \cdot C \begin{array}{l} \nearrow H \\ \searrow O \end{array}$ , by alkaline perman-

ganate or dichromate and sulphuric acid, although in the latter case esters are frequently formed as by-products, or by the oxygen of the air in presence of platinum or of nitrogenous

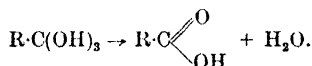


substances, e.g. acetic acid from alcohol. With aldehydes milder oxidizing agents can be used, e.g. alcoholic silver nitrate, per-acids,  $\text{HgO}$ , or bromine water (cf. Monosaccharides). The acids thus formed contain the same number of carbon atoms as the alcohol or aldehyde. Many complex carbon compounds, e.g. ketones with hypobromite, unsaturated compounds with permanganate, &c., yield acids containing a smaller number of carbon atoms. The higher acids of this series are converted into their lower homologues when oxidized.

2. Several acids have been prepared from the halogen compounds containing the group  $\cdot\text{CX}_3$ , e.g.:



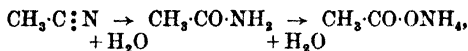
The trihydroxy compounds  $\text{R}\cdot\text{C}(\text{OH})_3$  which may be first formed are unstable and eliminate water yielding the acid:



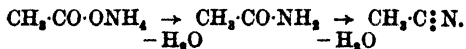
But derivatives of these trihydric alcohols, or **ortho-acids** as they are termed, are known; for example, **ethyl ortho-formate**,  $\text{HC}(\text{OC}_2\text{H}_5)_3$ , a neutral liquid of aromatic odour, insoluble in water, and boiling at  $146^\circ$ .

3. From the alkyl cyanides or nitriles,  $\text{C}_n\text{H}_{2n+1}\text{CN}$ . The cyanides, which are prepared by warming the alkyl iodides with cyanide of potassium, are converted into the fatty acids and ammonia by hydrolysis with potassium hydroxide solution, with dilute or concentrated hydrochloric acid, or with sulphuric acid diluted with its own volume of water.

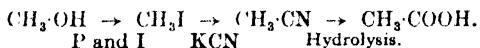
The reaction may be regarded as the addition of two molecules of water to each molecule of nitrile:



first yielding the acid amide, and then the ammonium salt of the acid, which is decomposed by the hydrolysing agent employed. The process, in the case of aromatic nitriles, can be stopped at the point when the acid amide is formed, but in the aliphatic series this is almost impracticable. The reaction is the exact reverse of the formation of nitriles from the ammonium salts of fatty acids:



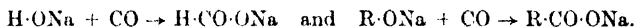
The great importance of this reaction, by means of which it is possible to obtain an acid  $C_{n+1}$  from an alcohol  $C_n$ , has been already indicated (p. 112). And since the acids can be converted indirectly by reduction into the corresponding alcohols, it is thus possible to build up synthetically, step by step, the alcohols richer in carbon from those poorer in carbon, a circumstance which is of especial importance in the case of the normal alcohols (*Lieben and Rossi*). As an example:



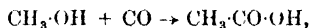
The acid may be converted into the alcohol containing the same number of carbon atoms by one of the following methods: (a) Ca salt + Ca formate  $\rightarrow$  aldehyde  $\rightarrow$  alcohol; (b) acid chloride reduced gives alcohol; (c) ethyl ester reduced gives alcohol.

4. Several methods are available for the introduction of the carbonyl group into a compound.

(a) By the action of carbon monoxide on a solid alkali hydroxide or alkyl oxide.



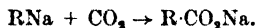
Carbon monoxide can be made to combine with the alcohol



at temperatures of about  $350^\circ$  and pressures of 200 atm. with a catalyst composed of phosphoric acid with a little copper phosphate. Methyl ether is formed as a by-product and the yields of acids tend to decrease with higher alcohols (*Hardy*, J. C. S., 1934, 1335; 1936, 355, 364).

Ammonium formate is also obtained by reducing ammonium carbonate solution with sodium amalgam.

(b) By the addition of  $\text{CO}_2$  to a metallic alkyl compound at a suitable temperature (*Wanklyn*):



The method is of interest in the case of the sodium derivatives of acetylenes.

(c) *Grignard's* reagents may be used in place of the metallic alkyls. On passing carbon dioxide into the ethereal solution a compound  $\text{R}\cdot\text{CO}_2\cdot\text{MgBr}$  is formed, and this with dilute

sulphuric acid gives the carboxylic acid,  $R \cdot CO_2H$ . (C. R., 1904, 138, 1048; also Org. Syn., 1925, 73.)

(d) The  $\cdot CO_2Et$  group can be introduced by treating an alkyl halide with ethyl chloroformate and sodium (*Wurtz*).



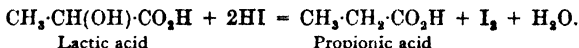
As a rule the yields are poor.

(e) An indirect method is to replace halogen by the nitrile group (Chap. IV, C.), and hydrolyse:



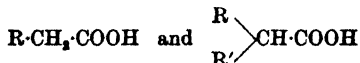
5. By the addition of hydrogen to unsaturated acids, e.g. propionic acid,  $CH_3 \cdot CH_2 \cdot CO_2H$ , from acrylic acid,  $CH_2 : CH \cdot CO_2H$ . This addition of hydrogen may be effected (a) directly by hydriodic acid and phosphorus, sodium amalgam and water, or by the aid of hydrogen and reduced nickel at a temperature of about  $100^\circ$ , or hydrogen and colloidal palladium at the ordinary temperature, Chap. XLIX, A.; (b) indirectly, by addition of hydrobromic acid and inverse substitution. Unsaturated acids also yield saturated ones containing fewer carbon atoms when fused with potash, e.g. 1 mol crotonic acid,  $C_4H_6O_2$ , yields 2 mols acetic acid,  $C_2H_4O_2$ .

6. From the hydroxy acids, by reduction with hydriodic acid:



7. From many polybasic acids, by the elimination of  $CO_2$ , for example, formic from oxalic,  $COOH \cdot COOH$ , and acetic from malonic,  $CO_2H \cdot CH_2 \cdot CO_2H$ .

8. *Aceto-acetic ester syntheses*.—The homologues



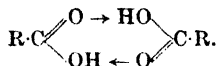
can be prepared from acetic acid by first converting the latter into aceto-acetic ester,  $CH_3 \cdot CO \cdot CH_2 \cdot COOC_2H_5$ , introducing alkyl groups into this, and then decomposing the compound so obtained by concentrated alcoholic potash. (Cf. Aceto-acetic Ester, Chap. IX, G.; and Malonic Ester, Chap. X.)

*Separation*.—Natural fats are nearly all glycerides, i.e. esters derived from the trihydric alcohol, glycerol, and various fatty

and other acids, so that a mixture of acids is obtained when any natural fat is hydrolysed. This mixture may be separated into its components as follows:

(a) By fractional distillation in a good vacuum; (b) by fractional precipitation of an alcoholic solution of the acids by means of magnesium acetate, calcium chloride, &c., the acids richer in carbon being precipitated first; (c) by fractional solution: the dry barium salts of formic, acetic, propionic, and butyric acids are very differently soluble in alcohol, the solubility increasing rapidly with the number of carbon atoms; (d) by fractional neutralization, and distillation of the non-combined acid.

*Behaviour.*—1. *Salts.* The acids are monobasic, and thus form **normal salts**, e.g.  $\text{CH}_3\cdot\text{CO}_2\text{Na}$ . They also yield **acid salts**—the so-called **per-acid salts**—from the existence of which we might feel inclined to doubt their monobasic nature. These salts can, however, be crystallized from a strongly acid solution only; they decompose on the addition of water, and also lose their excess of acid when heated. The formation of such acid salts is now usually regarded as being due to co-ordinate links, e.g.:



All the other chemical characteristics of the acids go to prove their monobasicity, especially the non-formation of acid esters.

2. The monobasic acids give rise to different groups of derivatives in much the same manner as the monohydric alcohols. The typical hydrogen atom is replaceable by an alkyl group with formation of an **ester** or **alkyl salt**, e.g.  $\text{CH}_3\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , ethyl acetate, or by a second acid radical with formation of an **anhydride**; the hydroxyl may further be replaced by halogen, especially chlorine, to an **acid chloride**, by SH to a **thio-acid**, by  $\text{NH}_2$  to an **amide**, &c. (See Acid Derivatives, Chap. VII.)

3. Halogens act upon the acids as substituents (Chap. VI, D.).

4. When the alkali salts are heated with soda lime, or frequently when the silver salts are heated alone, carbon dioxide is eliminated and a paraffin formed (see e.g. Methane). Paraffins are also formed when the alkali salts are electrolysed (see Ethane). Certain free acids, e.g. nitro-acetic acid lose carbonic anhydride when heated.

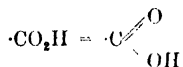
5. Most of the acids are relatively stable towards oxidizing agents, formic acid alone being readily oxidized to carbonic acid, and thus possessing strong reducing properties.

6. When the lime salts of the acids are heated with calcium formate they are reduced to aldehydes, and when heated for a lengthened period with hydriodic acid and phosphorus, to paraffins. When a mixture of the acid and formic acid is passed over  $\text{TiO}_2$  at  $250\text{--}300^\circ$ , an aldehyde is formed.

6a. When the lime salts are distilled alone, or when the higher acids are heated with phosphorus pentoxide, they are transformed into the ketones,  $(\text{C}_{n-1}\text{H}_{2n-1})_2\text{CO}$ .

7. The acids are not readily reduced to the corresponding aldehydes or primary alcohols. They may be reduced indirectly: (a) conversion into the acid chloride and catalytic reduction of this with palladized barium sulphate or kieselguhr to the aldehyde; (b) conversion to ester or reduction of this by the *Bouveault* and *Blaise* method (p. 203 and Chap. XLVII, A b) to the alcohol.

*Constitution.*—It follows from their modes of formation, especially 3, 4, and 6, and also from their behaviour (see 4 above), that acetic acid and its higher homologues contain alkyl radicals. The conversion of the alcohols into acids containing 1 atom of carbon more, by means of the cyanides, is especially strong proof of this. The latter contain the alkyl radical bound to the nitrile group  $\cdot\text{C}:\text{N}$ , and when they are hydrolysed the alkyl radical remains unchanged, and the tervalent nitrogen is replaced by  $\text{O}''$  and  $(\text{OH})'$ , both of these attaching themselves to the carbon atom of the original cyanogen, and so forming the group

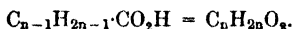


Consequently all the oxygen in the acid is united to a single carbon atom in the form of the group  $\text{CO}_2\text{H}$ . This group, which is termed carboxyl, is characteristic of the existence of acid properties. Further proof of the presence of the carboxyl group is based largely on the reactions of the acids. The alkyl group which they contain must be directly attached to C, as it is not removed by the action of acids or alkalis. We thus have  $\text{C}_n\text{H}_{2n+1}\cdot\text{C}$ . The presence of an OH group follows from the reaction of the acids with  $\text{PCl}_3$  or  $\text{PCl}_5$ , when an atom of O and an atom of H become replaced by an atom of

Cl, and they must presumably therefore be present in the form of the univalent  $\cdot\text{O}\cdot\text{H}$  group. There is only 1 oxygen atom left over to account for, and this is presumably attached to the

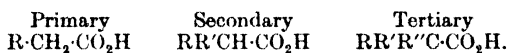
C by a double bond, and thus we have  $\text{C}_n\text{H}_{2n+1}\cdot\text{C}\begin{array}{l} \text{O} \\ \parallel \\ \text{OH} \end{array}$ . The

monobasic acids may therefore be regarded as compounds of the alkyl radicals with carboxyl, or, in other words, as derived from paraffins by the replacement of one hydrogen atom by a carboxyl group, thus:



Formic acid is, in this way, the hydrogen compound of carboxyl,  $\text{H}\cdot\text{CO}_2\text{H}$ .

The acids are distinguished as *primary*, *secondary*, or *tertiary*, according as the alkyl radicals which they contain are primary, &c. Thus:



There is no room for doubt that it is the hydrogen atom of the carboxyl group, the so-called "typical" hydrogen atom, which is replaced by metals in the formation of salts, for the foregoing acids are all monobasic, and consequently the number of hydrogen atoms present in the alkyl radical is of no moment for the acid character. In the di- and polybasic acids, the presence of two or more carboxyls can usually be demonstrated.

If the composition of the primary alcohols,  $\text{R}\cdot\text{CH}_2\cdot\text{OH}$ , is compared with that of the corresponding acids,  $\text{R}\cdot\text{CO}\cdot\text{OH}$  ( $\text{R}$  = alkyl or hydrogen), the latter are seen to be derived from the former by the exchange of two atoms of hydrogen for one atom of oxygen. The character of the original substance is thus appreciably changed by the entrance of the electro-negative (acidifying) oxygen in place of hydrogen.

*Nomenclature.*—The names for the first five acids are special; from  $\text{C}_6$  onwards, with a few exceptions, the names for the *normal* acids indicate the number of carbon atoms, e.g. hexoic, heptoic, or heptylic, &c. The systematic name (Geneva Congress) of the normal compound is obtained by adding the word acid to the name of the paraffin containing the same number of carbon atoms, e.g. acetic acid = ethane acid.

The monovalent radicals left when OH is removed from the molecule of each acid are often spoken of as **acid** or **acyl radicals**. (Cf. Alkyl Radicals.) The commonest of these radicals are  $\text{CH}_3\cdot\text{CO}\cdot$ , **acetyl**;  $\text{C}_2\text{H}_5\cdot\text{CO}\cdot$ , **propionyl**;  $\text{C}_3\text{H}_7\cdot\text{CO}\cdot$ , **butyryl**; &c.

The aldehydes may be looked upon as hydrogen compounds of the acyl radicals, and the ketones as compounds of the latter with alkyl radicals, thus:



The constitution of aldehydes and ketones, and of compounds derived from them, is based on the constitution of the monobasic acids.

*Isomers.*—The acids of the acetic series show the same isomerism as the alcohols containing 1 atom of carbon less, since they are formed from these by means of the cyanides. Thus we have 1 propionic acid, 2 butyric acids corresponding with the 2 propyl alcohols, 4 valeric acids corresponding with the 4 butyl alcohols, and so on.

**Formic acid** (*Methane acid*), *acidum formicicum*,  $\text{CH}_2\text{O}_2$  (*Samuel Fisher* and *John Wray*), 1670; *Marggraf*), occurs free in ants, especially *Formica rufa*, in the processionary caterpillar (*Bombyx processionea*), in the bristles of the stinging nettle, the fruit of the soap-tree (*Sapindus saponaria*); also in small quantity in perspiration, urine, and the juice of flesh.

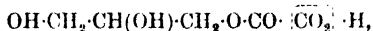
*Formation.*—From  $\text{HCN}$ ,  $\text{CHCl}_3$ ,  $\text{CH}_3\text{OH}$ ,  $\text{CO}_2$ , &c. (See General Methods of Formation.) Its salts are obtained by the reducing action of sodium amalgam upon ammonium carbonate or solutions of the alkali hydrogen carbonates (*Lieben*); the free acid by the dry distillation or oxidation of many organic substances, e.g. starch (*Scheele*).

*Preparation.*—1. Sodium formate is manufactured by absorbing carbon monoxide with lump caustic soda at 100–120° under pressure. For kinetics of the reaction, see *Bredig*, *Z. Elek.*, 1914, **20**, 489.

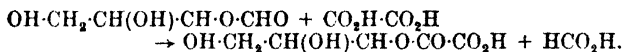
2. When oxalic acid is heated, formic acid is obtained in small quantity together with carbon monoxide, carbon dioxide, and water, and the same effect is produced by the direct action of sunlight upon its aqueous solution containing uranic oxide:



This decomposition is best effected by heating crystallized oxalic acid with glycerol to  $100^{\circ}$ – $110^{\circ}$  (*Berthelot, Lorin*), and adding more oxalic acid crystals as soon as the evolution of carbon dioxide ceases. The reaction can be repeated a number of times, and relatively large amounts of formic acid are produced from oxalic acid by the use of a relatively small amount of glycerol. The first product is a mon-oxalate of glycerol,



which then decomposes into  $\text{CO}_2$  and **glyceryl monoformate** or **monoformin**,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{O}\cdot\text{CHO}$  (cf. glyceryl esters). The addition of more oxalic acid liberates formic acid, and this distils over with the water from the crystals added, and glyceryl monoxalate is reformed. (*Chattaway, J. C. S., 1914, 151.*)



The anhydrous acid is obtained by decomposing the solid lead or copper salt with sulphuretted hydrogen.

*Properties.*—It is a colourless liquid which solidifies in the cold and fumes slightly in the air. M.-pt.  $+9^{\circ}$ ; b.-pt.  $101^{\circ}$ ; sp. gr. 1.22. It has a pungent acid and ant-like odour, acts as a powerful corrosive, and produces sores on the soft parts of the skin. It is a much stronger acid than acetic acid, is a powerful antiseptic, and decomposes completely into carbon monoxide and water when heated with concentrated sulphuric acid:  $\text{CH}_2\text{O}_2 = \text{CO} + \text{H}_2\text{O}$ .

*Salts.*—**Potassium-**,  $\text{HCO}_2\text{K}$ , **sodium-**,  $\text{HCO}_2\text{Na}$ , and **ammonium formate**,  $\text{HCO}_2\text{NH}_4$ , form deliquescent crystals. The first two yield oxalates when strongly heated, with evolution of hydrogen (see Oxalates); the ammonium salt yields formamide and water at  $180^{\circ}$ :



The **lead** salt,  $\text{Pb}(\text{HCO}_2)_2$ , forms glistening, sparingly soluble needles, the **copper** salt,  $\text{Cu}(\text{HCO}_2)_2 + 4\text{H}_2\text{O}$ , large blue monoclinic crystals, and the **silver** salt colourless crystals. The last-mentioned deposits silver when warmed, consequently a solution of nitrate of silver is reduced when heated with formic acid.



A solution of the soluble **mercuric salt**,  $\text{Hg}(\text{HCO}_2)_2$ , evolves carbon dioxide when gently warmed, and yields free formic acid together with the sparingly soluble **mercurous salt**,  $\text{Hg}_2(\text{HCO}_2)_2$ , which separates in white plates; on further heating, carbon dioxide, formic acid, and metallic mercury are obtained. Similarly an aqueous solution of mercuric chloride is reduced by formic acid to the mercurous salt,  $\text{Hg}_2\text{Cl}_2$ .

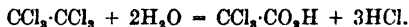
Formic acid unlike its homologues is thus a strong reducing agent, due to the presence of the  $\cdot\text{CHO}$  group, i.e.  $\text{HO}\cdot\text{C}\begin{array}{l} \nearrow \text{O} \\ \searrow \text{H} \end{array}$ .

It decomposes into carbonic acid and hydrogen when heated alone to  $160^\circ$ , or when brought into contact with finely-divided rhodium.

**Acetic acid** (*Ethane acid*),  $\text{CH}_3\cdot\text{COOH}$ , was known in the dilute form, as crude wine vinegar, to the ancients. *Stahl* prepared the concentrated acid about 1700. *Glauber* mentions wood vinegar (1648). Its constitution was established by *Berzelius* in 1814. Salts of acetic acid are found in various plant juices, especially those of trees, and in the perspiration, milk, muscles, and excrements of animals. Esters of acetic acid also occur, e.g. triacetin in croton-oil (see p. 183, and also under Glycerol).

*Formation* (see p. 165 *et seq.*).—It is the final product of the oxidation of a great many compounds, and also of their treatment with alkalis.

The following synthesis is of historical interest: Perchloroethylene,  $\text{CCl}_2\cdot\text{CCl}_2$ , which is prepared from  $\text{CCl}_4$ , i.e. from  $\text{Cl}$  and  $\text{CS}_2$ , yields with chlorine in presence of water in direct sunlight trichloroacetic acid, carbon hexachloride,  $\text{C}_2\text{Cl}_6$ , being obviously formed as intermediate product (*Kolbe*, 1843).



The latter acid is reduced to acetic acid by nascent hydrogen (*Melsens*).

*Manufacture*.—1. *From alcohol*.—A dilute aqueous solution of alcohol, containing up to 15 per cent, is slowly converted into acetic acid on exposure to the oxidizing action of the air and in presence of certain low forms of plant life known as bacteria, especially *Bacterium aceti*, of which there are many varieties. These organisms are contained in the air, and hence

become deposited in alcoholic liquors exposed to the air, and thus produce the souring of wines, &c. For the growth of the micro-organisms, nitrogenous matter, phosphates, &c., are essential, and hence pure alcohol mixed with water does not turn sour. In the "quick process" dilute alcoholic liquors, e.g. waste wine liquors or alcoholic malt wash, are allowed to trickle over beechwood shavings which have been previously coated with the required bacteria (mother of vinegar), and the temperature is kept at about 35°.

Vinegar is an aqueous solution of acetic acid, usually containing only 4 to 6 per cent, but containing also small quantities of alcohol, of the higher acids, e.g. tartaric and succinic, the ethyl esters of the acids, proteins, &c.

2. *From wood*.—The dry distillation of wood, which is conducted in cast-iron retorts, yields: (1) gases, e.g. hydrogen 15 per cent, methane 11 per cent, carbon dioxide 26 per cent, carbon monoxide 41 per cent, and higher hydrocarbons 7 per cent; (2) an aqueous solution known as pyroligneous acid, which in addition to acetic acid, contains methyl alcohol, acetone, methyl ethyl ketone, homologues of acetic acid, and strongly smelling combustible products (empyreuma); and (3) wood-tar, which contains compounds of the nature of carboic acid. The pyroligneous acid is worked up for acetic acid by converting it into the sodium or calcium salt, heating these—the former to fusion, and the latter to 200°, and then distilling with sulphuric acid.

In modern distilleries the acetic acid is recovered direct from the crude pyroligneous acid by fractional distillation or by a process of scrubbing with a suitable solvent.

3. *Synthetic acetic acid*.—Large quantities of the acid are now made from acetaldehyde obtained from acetylene (Chap. I, C., and LI, F.). The oxidation is carried out in aluminium-lined vessels with atmospheric oxygen in presence of manganese acetate as catalyst.

*Properties*.—Acetic acid is a strongly acid liquid of pungent odour, which feels slippery to the touch and burns the skin, and which solidifies on a cold day to large crystalline plates melting at 16.6° (glacial acetic acid). It boils at 118°, and its vapour burns with a blue flame; sp. gr. at 15° = 1.055. When mixed with water, contraction and consequent increase in density ensue, the maximum point corresponding with the hydrate  $\text{CH}_3\cdot\text{CO}_2\text{H} + \text{H}_2\text{O} = \text{CH}_3\cdot\text{C}(\text{OH})_3$  (ortho-acetic acid), which

contains 77 per cent acid and has a sp. gr. of 1.075 at 15.5°; after this, the specific gravity decreases with further addition of water, so that a 50-per-cent acid has almost the same density as one of 100 per cent. The amount of acid present in a solution is determined either by its sp. gr., this contraction being borne in mind, or by titration with standard alkali, using phenolphthalein as indicator, or with very concentrated acid by a careful determination of its melting- (freezing-) point in the *Beckmann* apparatus. The vapour density near the boiling-point is much higher than that required by theory, but is normal above 250°. The high values are due to the association of the molecules at the lower temperatures, and in the liquid state the molecular formula is undoubtedly  $(C_2H_4O_2)_x$ , &c. The acid is hygroscopic, and stable towards chromic acid and cold permanganate of potash. It dissolves phosphorus, sulphur, and many organic compounds, is corrosive, and gives rise to painful wounds on tender parts of the skin.

*Salts.*—All the normal acetates are soluble in water. The following **potassium** salts are known: (a)  $KC_2H_3O_2$ , (b)  $KC_2H_3O_2 \cdot HC_2H_3O_2$ , and (c)  $KC_2H_3O_2 \cdot 2HC_2H_3O_2$ .

**Sodium acetate**,  $CH_3 \cdot COONa$ ,  $3H_2O$ , forms transparent readily soluble rhombic prisms. **Ammonium acetate**,  $CH_3 \cdot CO \cdot NH_4$ , resembles the potassium salt. It is used in medicine as a sudorific (liquor ammonii acetici). Its solution loses ammonia on evaporation, and it yields acetamide when distilled. **Ferrous acetate**,  $Fe(C_2H_3O_2)_2$ , is largely used in the form of "iron liquor" as a mordant in dyeing. The normal **ferric** salt,  $Fe(C_2H_3O_2)_3$ , which is employed for the same purpose, is obtained when a soluble ferric salt is mixed with sodium acetate. Its solution is deep red in colour, and deposits the iron as **basic salt**,  $CH_3 \cdot CO \cdot OFe(OH)_2$ , when heated with excess of water. It is used in medicine as "liquor ferri acetici". The analogous **aluminium acetate** is known only in solution, and finds a wide application as "red liquor" mordant in calico printing and dyeing. Its use depends upon the fact that it is readily hydrolysed by water, e.g. when exposed to the action of steam, and on the insolubility of the compound (lake) formed from the residual alumina and the colouring matter. It is employed in small doses as an astringent in cases of diarrhœa, &c. Lead salts. (1) **Normal lead acetate** or sugar of lead,  $(CH_3 \cdot COO)_2Pb + 3H_2O$ , is manufactured from sheet-lead and acetic acid. It forms colourless lustrous

four-sided prisms, which are poisonous and of a nauseous sweet taste. It combines with lead oxide to (2) **basic salts of alkaline reaction**, termed sub-acetates.

The simplest basic salt has the composition  $\text{OH}\cdot\text{Pb}\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ , but there also exist others, e.g.  $\text{OH}\cdot\text{Pb}\cdot\text{O}\cdot\text{Pb}\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ , &c. Two molecules of acetic acid can combine with as many as 5 molecules of lead oxide. These basic acetates are used as *Goulard's* lotion, and on the large scale for the preparation of white-lead, &c.

**Cupric acetate**,  $\text{Cu}(\text{C}_2\text{H}_3\text{O}_2)_2 + 2\text{H}_2\text{O}$ , dark-green crystals, also forms basic salts, e.g. *verdigris*  $\text{OH}\cdot\text{Cu}\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ . **Silver acetate**,  $\text{AgC}_2\text{H}_3\text{O}_2$ , forms characteristic glistening needles.

*Detection of Acetic Acid.*—(1) When an acetate is heated with alcohol and sulphuric acid, the pleasant-smelling ethyl acetate is formed; (2) by means of the silver salt; (3) by the odour of cacodyl produced upon heating the potassium or sodium salt with arsenious oxide. (See p. 134.)

**Propionic acid**,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  (*Gottlieb*, 1844), may be obtained by the reduction of acrylic or lactic acid (see p. 168); also from lactate or malate of calcium by suitable *Schizomyces* fermentation (*Fitz*). It is usually prepared by the oxidation of propyl alcohol with dichromate mixture (See p. 165.)

It separates from its aqueous solution as an oil on the addition of calcium chloride, hence the name  $\pi\rho\omega\tau\omicron\varsigma$ , the first, and  $\pi\acute{\iota}\omega\nu$ , fat; the first oily acid.

**Butyric acids**,  $\text{C}_4\text{H}_8\text{O}_2$ .

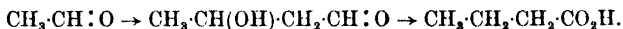
1. **Normal butyric acid**, *butane acid*, *ethylacetic acid*,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , occurs free in perspiration, in the juice of flesh, in the contents of the large intestine, and in the solid excrements; as hexyl ester in the oil of the fruit of *Heracleum giganteum*, as octyl ester in *Pastinaca sativa*, and to the extent of 2 per cent as glyceride in butter (*Chevreul*, 1822).

*Formation.*—(See also General Modes of Formation.) It is produced (1) by the decay of moist fibrin and of cheese (being therefore contained in Limburg cheese); (2) by a *Schizomyces* fermentation of glycerol, and of carbohydrates (*Pelouze* and *Gélis*; *Fitz*; see below); (3) by the oxidation of proteins, with chromic acid, of fats with nitric acid, of coniine, &c., and (4) by the dry distillation of wood.

*Preparation.*—In the "butyric fermentation" of sugar or starch by anaerobic bacteria, derived from sour milk or decaying

cheese (e.g. *Bacillus butylicus*, *B. amylobacter*, *Clostridium butyricum*),  $\text{CaCO}_3$  or  $\text{ZnO}$  being added at the same time, to neutralize the acid formed, otherwise the fermentation would stop. The optimum temperature is  $30\text{--}35^\circ$  and the time required is 8–10 days.

Acetaldehyde is probably an intermediate product which yields lactic aldehyde and finally butyric acid:



**Properties.**—It is a thick liquid of unpleasant rancid odour, in presence of ammonia like that of perspiration, is miscible with water, and separates from its aqueous solution on the addition of salts. B.-pt.  $163^\circ$ . The calcium salt,  $\text{Ca}(\text{C}_4\text{H}_7\text{O}_2)_2 + \text{H}_2\text{O}$ , forms glistening plates, and is characterized by being more soluble in cold than in hot water; it therefore separates on warming the concentrated cold aqueous solution. On prolonged heating of the solution, however, it is transformed into the calcium salt of isobutyric acid.

2. **Isobutyric acid**, 2-methyl-propane acid, dimethyl-acetic acid,  $(\text{CH}_3)_2\cdot\text{CH}\cdot\text{CO}_2\text{H}$ , is present in the free state in the carob (*Redtenbacher*), in the root of *Arnica montana*, and as esters in *Pastinaca sativa* and Roman chamomile oil.

It is obtained from isopropyl cyanide (*Erlenmeyer*), by the oxidation of isobutyl alcohol, by the aceto-acetic ester synthesis (Chap. IX, H.), &c. It resembles *n*-butyric acid, but is more sparingly soluble in water (1 in 5), and boils  $9^\circ$  lower, i.e. at  $154^\circ$ . Unlike the latter, however, it is easily oxidized to acetone or acetic acid, and carbonic acid. The calcium salt,  $\text{Ca}(\text{C}_4\text{H}_7\text{O}_2)_2$ , differs from its isomer in being more soluble in hot water than in cold. The solution is accompanied by a slight absorption of heat, whereas the solution of the salt of the *n*-acid is accompanied by a slight evolution of heat.

**Valeric acid**,  $\text{C}_5\text{H}_{10}\text{O}_2$ , exists in the four modifications which are theoretically possible:

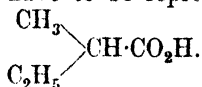
1. **Normal Valeric acid** (*Pentane acid*), propyl-acetic acid,  $\text{CH}_3\cdot(\text{CH}_2)_3\cdot\text{CO}_2\text{H}$ , from normal butyl cyanide (*Lieben* and *Rossi*, 1871), is best prepared from propyl-malonic acid. (See B., 1888, Ref. 649; also malonic ester synthesis.) It boils at  $185^\circ$ , and is soluble in 27 parts of water.

2. **Isovaleric acid**, 3-methyl-butane acid, isopropyl-acetic acid,  $(\text{CH}_3)_2\cdot\text{CH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , is obtained from isobutyl cyanide. It is found in the free state and in the form of esters in the animal

kingdom and in many plants, especially (free) in the valerian root (*Valeriana officinalis*), and in the angelica root (*Angelica archangelica*), from which it is obtained by boiling with soda; further, in the blubber of the dolphin (*Chevrul*, 1817), in the berries of *Viburnum opulus*, in the perspiration from the foot, &c. The natural acid is usually mixed with the active valeric acid, and is therefore optically active; the oxidation of fermentation amyl alcohol by chromic acids yields a similar mixture. When pure it is optically inactive, boils at 175°, and has an unpleasant pungent acid odour, like that of old cheese, and a corrosive action. It is used in medicine.

3. **Methyl-ethyl-acetic acid**, *active valeric acid*, *2-methyl-butane acid*,  $\begin{array}{c} \text{CH}_3 \\ \text{C}_2\text{H}_5 \end{array} \rangle \text{CH} \cdot \text{CO}_2\text{H}$ , occurs in nature, as already mentioned, and results from the oxidation of the active (–) amyl alcohol; it is in this case (+) optically active, while, if prepared synthetically, e.g. by the aceto-acetic ester reaction, it is optically inactive, but can be resolved by suitable methods into a + valeric acid and a – valeric acid. [For determination of optical activity, see section on Physical Properties, Chap. LXXI, I.]

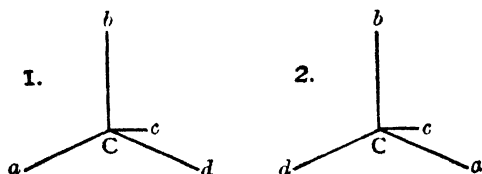
There are thus three distinct acids, one dextro-rotatory, one lævo-rotatory, and the third optically inactive, which have to be represented by the same structural formula, viz.



As regards their ordinary chemical and physical properties, the two active acids are exactly alike, and differ only in their action on polarized light. This difference is not due to the different arrangements of the molecules, as all three are liquids, and in liquids the molecules are not usually regarded as having definite arrangements. A further proof that the cause of the activity, and hence of the isomerism, is to be sought for in the molecules themselves, and not in any special arrangements of the molecules, is the fact that the optical properties of the acids in the gaseous state are similar to those in the liquid. The investigations of *Pasteur*, *Le Bel*, and *Van't Hoff* have shown that this kind of isomerism, which is now usually termed **stereo-isomerism**, is due to the fact that the compound contains a carbon atom to which 4 different radicals

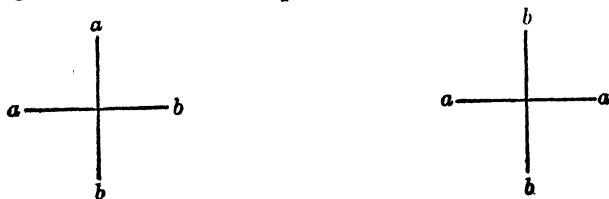
are attached; in the case of valeric acid these are, H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{CO}_2\text{H}$ . Such a carbon atom is usually termed an asymmetric carbon atom. (This expression does not mean that the carbon atom itself is asymmetric in shape, but that it is attached to four distinct radicals, an arrangement which produces a dissymmetric molecule.)

*Van't Hoff* showed that if these radicals are arranged around the carbon atom, not in a single plane, but in the three dimensions of space, then every compound containing a single asymmetric carbon atom should exist in the modifications represented by the figures 1 and 2.

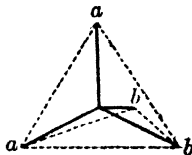


Such modifications are not identical, since they cannot be brought to superposition (this can be shown readily by the aid of models), but they are very similar; in fact, they stand in the relationship of the right to the left hand, or in the relationship of an asymmetric object to its mirror image. They are enantiomorphous.

The spatial relationship of the radicals is often expressed by stating that if the asymmetric carbon atom is situated as the centre of a regular tetrahedron, then the four radicals occupy the solid angles of the tetrahedron. The arguments in favour of the spatial representation of the molecules of carbon compounds are largely based on a consideration of the number of isomeric forms in which simple carbon derivatives occur. For example, no simple compound of the type  $\text{Caabb}$  is known to exist in more than one modification. If, however, the radicals and carbon atom were arranged in a single plane, we should expect the two modifications:



but with the spatial or tetrahedral arrangement we can get but the one modification.



An examination of models \* will clearly show that in whatever way the radicals *a* and *b* are exchanged a model is obtained which can be superimposed on the one depicted.

Similarly with regard to compounds  $\text{C} a a b c$ , in which 2 of the 4 radicals are alike. The tetrahedral arrangement allows of one modification only, and in these cases only one is actually known. When, however, all four radicals are distinct, e.g.  $\text{C} a b c d$ , the spatial arrangement admits of two enantiomorphous or non-superposable **configurations**, which are in the relationship of object to mirror image, and these two modifications represent the two optically active isomerides, in which almost every compound of the type  $\text{C} a b c d$  has been shown to exist. An examination of the models representing the two modifications shows that they are both dissymmetric, i.e. a plane of symmetry cannot be drawn through them, and the optical activity which such compounds exhibit when in the liquid state, or in solution, is undoubtedly connected with the dissymmetry of their molecules. Since the two configurations contain the same radicals and are very similar, in the one case containing the 4 radicals, arranged in what we may term a positive, and in the other, in the opposite or negative direction, it follows that the molecules of the two compounds should produce rotations of the polarized ray equal in magnitude but of opposite sign. This is the case with the two optically active valeric acids: the pure dextro-acid has a rotation of  $+17.85^\circ$ , and the lævo-acid  $-17.85^\circ$ .

In addition to the two optically active modifications, a third isomeride is usually known which is optically inactive. As it can be synthesized by mixing together equal weights of the

\* In using models it must be remembered that the models are not supposed to represent in the least the actual shapes of the atoms, but merely their spatial relationships. It must also be borne in mind that the atoms and radicals in the molecules are in a state of motion, and the fixed position represented in the model may be supposed to represent the mean position or the position which the centre of gravity would occupy at absolute zero.



*d* and *l* compounds, it follows that such a compound is either a mixture or a definite compound of the two active isomerides, i.e. its optical inactivity is owing to the fact that the two components are present in equal quantities. Such isomerides are often spoken of as **racemic compounds**, and are **optically inactive by external compensation**. Such racemic compounds may be resolved into their optically active components by several methods, most of which were devised by *Pasteur*. (See Racemic Acid, Chap. X, D.)

*Relationship between Dissymmetry of the Molecule and Optical Activity*.—Since the two isomerides of the type C a b c d are optically active, it should follow that any derivative of valeric acid in which the four radicals attached to the central carbon atom are still different should be also optically active, but that a derivative in which two of the radicals become similar should become inactive. This question has been examined by *Le Bel* in the case of some forty derivatives of active amyl

alcohol, 
$$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{C}_2\text{H}_5 \end{array} \begin{array}{c} \text{H} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{CH}_2\text{OH} \end{array}$$
. The alcohol, its chloride, amine,

all its esters, its oxidation product, viz. valeric acid, and all its salts, esters, &c., are optically active; the hydrocarbon

$$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{C}_2\text{H}_5 \end{array} \begin{array}{c} \text{H} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{CH}_3 \end{array}$$
 obtained by reducing the chloride is, however, optically inactive, and cannot be resolved into active components.

4. **Trimethyl-acetic acid**, 2 : 2-dimethylpropane acid, *pivalic acid*,  $(\text{CH}_3)_3\text{C}\cdot\text{CO}_2\text{H}$ , can be prepared from tertiary butyl cyanide (*Butleroff*, 1873). It melts at  $35^\circ$ , boils at  $164^\circ$ , and has an odour like that of acetic acid.

Eight hexoic acids are theoretically possible, and of these seven are known. The most important is **normal caproic acid**,  $\text{CH}_3(\text{CH}_2)_4\cdot\text{CO}_2\text{H}$  (*Chevreul*, 1822), which is found in nature, e.g. in cocoa-nut oil, Limburg cheese, and as a glyceride in the butter made from goats' milk, and is produced in the butyric fermentation of sugar, and by the oxidation of albuminous compounds and of the higher fatty acids, &c. Like valeric acid, it has a persistent odour of perspiration and rancid butter. B.-pt.  $205^\circ$ .

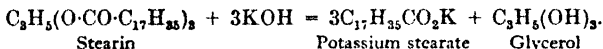
The higher acids found in nature mainly as glycerides are of normal type, and contain an even number of carbon atoms.

Goats' butter contains the acids  $C_6$ ,  $C_8$ , and  $C_{10}$ , hence the names **caproic**, **caprylic**, and **capric** acids, and cocoa-nut oil—in addition to those three—the acid  $C_{12}$ . This last, **lauric acid**, is contained more especially in oil of laurels (*Laurus nobilis*); **myristic**,  $C_{14}$ , is present in oil of iris and nutmeg butter (from *Myristica moschata*); **arachidic**,  $C_{20}$ , in ground-nut oil (*Arachis hypogaea*); **behenic**,  $C_{22}$ , in the oil of ben (*Moringa oleifera*); **lignoceric**,  $C_{24}$ , in the oil from *Adenanthera pavonina*; **cerotic**,  $C_{26}$ , forms in the free state the chief constituent of bees'-wax and as ceryl ester that of Chinese-wax. **Palmitic acid**,  $C_{16}H_{32}O_2$ , and **stearic acid**,  $C_{18}H_{36}O_2$ , are very widely distributed, being nearly always accompanied by a third acid poorer in hydrogen, viz. **oleic acid**,  $C_{18}H_{34}O_2$  (see Unsaturated Acids, Chap. VI, B.).

Most animal and vegetable fats and oils, e.g. tallow, suet, butter, palm, olive and seal oils, consist almost entirely of glycerides viz. the glyceryl esters of palmitic, stearic, and oleic acids; these esters being termed, for the sake of brevity, **tripalmitin**,  $C_3H_5(O\cdot CO\cdot C_{15}H_{31})_3$ , **tristearin**,  $C_3H_5(O\cdot CO\cdot C_{17}H_{35})_3$ , **triolein**,  $C_3H_5(O\cdot CO\cdot C_{17}H_{33})_3$ . The constitution of the fats was elucidated by *Chevreul* in 1811. In addition glycerides of acids more unsaturated than oleic are present in drying oils. (Cf. Chap. LV, Oils and Fats.)

Most of the varieties of wax are, on the contrary, esters of monohydric alcohols; thus bees'-wax consists of the **melissic ester of palmitic acid**,  $C_{30}H_{61}O\cdot CO\cdot C_{15}H_{31}$ , together with free **cerotic acid**, Chinese wax (from *Croton sebiferum*, the tallow-tree) of the ester  $C_{27}H_{55}O\cdot CO\cdot C_{26}H_{53}$ , and spermaceti (*Cetaceum*, in the skull of *Physiter macrocephalus*) of the ester  $C_{16}H_{33}O\cdot CO\cdot C_{15}H_{31}$ .

From all these esters the acids are obtained in the form of potassium salts by saponification with alcoholic potash, thus:



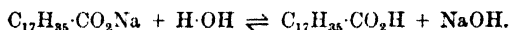
The separation of the acids is effected by fractional crystallization, fractional precipitation with magnesium acetate, or by fractional distillation either of the fats themselves or of their methyl esters in a high vacuum. Oleic acid can be separated from palmitic and stearic by taking advantage of the solubility of its lead salt in ether or alcohol.

The stearine candles of commerce consist of a mixture of

palmitic with excess of stearic acid, some paraffin wax being usually added to prevent them becoming crystalline. The manufacture of candles depends upon the saponification of the solid fats, especially of beef and mutton tallow, by means of water and lime, in autoclaves at 100–140°, of concentrated sulphuric acid at 110–120°, of super-heated steam at 200–240°, or of Twitchell's reagent obtained by sulphonating a mixture of oleic acid and naphthalene, probably  $\text{NaO}_3\text{S}\cdot\text{C}_{10}\text{H}_6\cdot\text{C}_{17}\text{H}_{31}\cdot\text{CO}_2\text{H}$ .

The glycerides are also hydrolysed to acids and glycerol by the **lipase** contained in crushed castor seed (Chap. LXIX, D.).

**Soaps** consist of the alkaline salts of palmitic, stearic, and oleic acids, hard soaps containing sodium salts, chiefly of the solid acids, while soft soaps contain potassium salts, principally oleate. By the addition of common salt to a solution of a potassium soap, the latter is converted into a sodium soap, which is insoluble in a solution of sodium chloride. This process is usually termed "*salting out*", and is analogous to the precipitation of sodium chloride by the addition of hydrogen chloride to its saturated solution. These alkali soaps dissolve to a clear solution in a little water, but with excess of water are hydrolysed to a certain extent, yielding free alkali and free fatty acid or acid salt, analogous to potassium peracetate. The cleansing action of soap is usually attributed to the presence of the small amount of free alkali thus formed:



This hydrolysis is similar to that observed in the case of inorganic salts derived from a feeble acid and a strong base, and increases with increasing dilution. The production of free alkali (or free hydroxyl ions) can be readily understood by aid of the theory of electrolytic dissociation. The calcium, barium, and magnesium salts are insoluble in water, but partly crystallizable from alcohol. The precipitates produced by the action of hard water on soaps consist largely of those insoluble salts. The lead salts (lead plaisters) are prepared by boiling fats with lead oxide and water.

Mixed glycerides are common constituents of many fats, e.g.  $\text{C}_3\text{H}_5(\text{O}\cdot\text{CO}\cdot\text{C}_{15}\text{H}_{31})(\text{O}\cdot\text{CO}\cdot\text{C}_{17}\text{H}_{35})_2$ . (See *Armstrong* and *Allan*, J. S. C. I., 1924, 207T.

For electrical conductivity of soap solutions, cf. *Banbury* and *Martin*, J. C. S., 1914, 417; *M'Bain* and *Martin*, *ibid.* 957, and for detergent action, cf. *Pickering*, *ibid.* 1917, 86.

The higher acids with an uneven number of carbon atoms,  $C_{11}$ ,  $C_{13}$ ,  $C_{15}$ , and  $C_{17}$ , are prepared synthetically from the acids  $C_nH_{2n+1}\cdot CO_2H$ , by transforming them into the ketones  $C_nH_{2n+1}\cdot CO\cdot CH_3$  (p. 155), and oxidizing these, when acids  $C_{n-1}H_{2n-1}\cdot COOH$  are obtained. (*Krafft*.)

On these reactions a method for proving that the higher fatty acids, e.g. palmitic and stearic, are normal in constitution has been based. (See the caution given on p. 157.)

The acid  $C_{15}H_{31}\cdot CO_2H$  is converted into the ketone  $C_{15}H_{31}\cdot CO\cdot CH_3$ ; this on oxidation yields  $C_{14}H_{28}\cdot CO_2H$  and acetic acid. The conversion into ketone and subsequent oxidation is repeated, and an acid,  $C_{13}H_{27}\cdot CO_2H$ , obtained. The processes are repeated until an acid,  $CH_3\cdot (CH_2)_7\cdot CO_2H$ , *n*-nonylic acid, is obtained. This can be shown to have a normal structure by synthetical methods, and hence all the higher acids must also have a normal structure, since if the acid  $C_{13}H_{27}\cdot CO_2H$  had not a normal structure, but contained a side chain, e.g.

$\begin{array}{c} CH_3 \\ \searrow \\ C_{11}H_{23} \end{array} \begin{array}{l} \nearrow \\ \nearrow \end{array} CH\cdot CO_2H$ , on conversion into the ketone and subsequent oxidation it would not yield the acid,  $C_{12}H_{25}\cdot CO_2H$ , but a ketone,  $CH_3\cdot CO\cdot C_{11}H_{23}$ , or the oxidation products of this ketone.

**Dissociation constant.** — One of the most characteristic physical constants of the organic acids is the dissociation constant  $K$ , which is involved in the equation  $K = \frac{a^2}{v(1-a)}$ , where  $v$  = volume of solution in litres containing 1 gm. mol. of the acid,  $a$  is the amount ionized, and  $1-a$  the amount not ionized. This equation is based on the law of mass action. In the case of a feeble organic acid, e.g. acetic acid, where 1 gm. molecule is dissolved in  $v$  litres of solution, a state of equilibrium represented by the equation  $CH_3\cdot COOH \rightleftharpoons CH_3\cdot COO + H$  occurs. Then if  $k_1$  and  $k_2$  represent the velocity constants of the direct and reverse actions, we have, according to *Guldberg* and *Waage's* law, at the stage of equilibrium:

$$k_1 \times \frac{1-a}{v} = k_2 \times \frac{a}{v} \times \frac{a}{v}, \text{ or } \frac{a^2}{v(1-a)} = \frac{k_1}{k_2} = K.$$

The extent of ionization in a solution containing 1 gm. molecule in  $v$  litres is determined by electrical conductivity

determinations.  $\alpha = \mu_v/\mu_\infty$ , i.e. the degree of ionization at a dilution  $v$  is the ratio of the molecular conductivity at this dilution to the molecular conductivity at infinite dilution when all the acid molecules are ionized. For a weak acid  $K$  remains constant, and affords a convenient measure of the strength of an organic acid. The values at  $25^\circ$  are:

Acid $K \times 10^5$	Formic	Acetic	Propionic	<i>n</i> -Butyric	<i>iso</i> -Butyric
	21.4	1.8	1.4	1.5	1.6

Formic acid is obviously much the strongest of the fatty acids, but they are all comparatively weak acids compared with the strong mineral acids. Close comparison cannot be drawn between the two groups, as the equation  $K = \frac{a^2}{(1-a)v}$  does not hold good for strong acids.

## B. Unsaturated Acids, $C_nH_{2n-2}O_2$ or $C_mH_{2m-1} \cdot CO_2H$

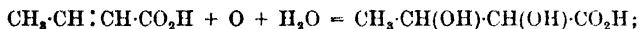
	Melting-pt.	Boiling-pt.
Acrylic acid, $C_3H_4O_2$ ..	$7^\circ$	$140^\circ$
Crotonic acids, $C_4H_6O_2$ $\left\{ \begin{array}{l} 1a \\ 1b \\ 2 \end{array} \right.$	72	182
	15	172
	16	160
Angelica acid } $C_5H_8O_2$ ..	45	185
Tiglic acid } ..	65	198
Oleic acid } $C_{18}H_{34}O_2$ ..	14	—
Elaidic acid } ..	45	—
Erucic acid } $C_{22}H_{42}O_2$ ..	33	—
Brassicic acid } ..	60	—

These acids are known as the acids of the **oleic series**. In their physical properties they closely resemble the saturated acids, apart from differences in melting-point, which are appreciable. They have the chemical characteristics of monobasic acids; they yield salts, esters, amides, &c., in much the same manner as the saturated acids; but in addition they resemble the olefines in the readiness with which they yield additive compounds with hydrogen, halogens, halogen hydrides, or hydrogen cyanide, thus forming fatty acids or their substitution derivatives. Thus oleic acid,  $C_{18}H_{34}O_2$ , when treated with  $H_2$  in presence of colloidal Pd, yields stearic acid,  $C_{18}H_{36}O_2$ , and with bromine, dibromo-stearic acid,  $C_{18}H_{34}Br_2O_2$ . In this

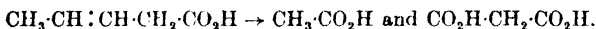
way they characterize themselves as derivatives of the unsaturated hydrocarbons of the ethylene series, from which they may be regarded as formed by the replacement of an atom of hydrogen by carboxyl. They may therefore be termed olefine-carboxylic acids.

Upon the addition of halogen hydride, the halogen does not always attach itself to that carbon atom to which the smaller number of hydrogen atoms is united (Chap. LI, B.).

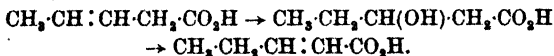
The presence of the double bonds renders them much more sensitive to oxidizing agents than are the fatty acids. When a very dilute oxidizing agent is employed, e.g. 1 per cent permanganate, dihydroxy derivatives of fatty acids are obtained:



but if stronger oxidizing agents are employed, a rupture of the molecule occurs at the position where the double bond exists, and a mixture of acids is obtained:



This affords an excellent method for determining the position of the double bond in the molecule of the acid. (Cf. also Ozonization, Chap. XLVIII, G.) Fusion with caustic alkalis also causes a breaking up of the molecules, and the formation of a mixture of fatty acids; but this reaction is of no use for determining the position of the double bond, as treatment with alkali tends to shift the double bond, if possible, nearer to the carboxylic group. *Fittig* (B., 1891, 82, &c.) has studied the action of dilute alkalis on a number of unsaturated acids, and always observed the same effect, e.g. the acid,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{COOH}$ , passes into  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}:\text{CH}\cdot\text{COOH}$  (2-hexene-1-acid). Such changes, which are termed "molecular transformations", are explained by the assumption that atoms or radicals (in this case the elements of water) are added on to the original compound, and then eliminated in a different manner, e.g.:

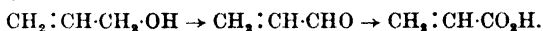


The presence of the double bond in the molecule has a considerable effect upon certain properties of the acid; for example, the dissociation constant and the rate of esterification by the catalytic method.

*Fichter* and *Pfister* have shown (Abs. 1904, i. 965) that the introduction of a double bond usually increases the strength of an acid, and that the effect is most marked when the double bond is in the  $\beta$ - $\gamma$ -position, e.g. the values for  $K \times 10^5$  are butyric acid 1.54, crotonic acid 2.0, and for vinyl acetic 3.83. (Cf. *Lowry*, Trans. Far., 1923, 500.)

*Sudborough* (J. C. S., 1905, 1840; 1907, 1033; 1909, 315, 975) has shown that the introduction of the double bond in the  $\alpha$ -position greatly retards esterification. The rates for hydrocinnamic,  $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CO_2H$ , and for cinnamic acid,  $C_6H_5 \cdot CH : CH \cdot CO_2H$ , are as 40 : 1. See also Chap. XXXVI, Steric Hindrance.

*Modes of Formation.*—1. By oxidizing the corresponding alcohols or aldehydes, e.g. acrylic acid from allyl alcohol or acrolein.



2. From the unsaturated alcohols or their iodides, by converting them into nitriles and hydrolysing these, e.g. crotonic acid from allyl iodide (intramolecular rearrangement, p. 189).



Both these methods of formation are analogous to those of the fatty acids.

3. From the monohalogen substitution products of the saturated fatty acids, by warming with alcoholic potash, sometimes upon simply heating with water. This reaction is analogous to the formation of the olefines from alkyl haloids; it occurs in the case of those substituted acids which contain the halogen in the  $\beta$ -position to the carboxyl (see p. 195 *et seq.*). or from dihalogen compounds, e.g.  $CH_3 \cdot CHBr \cdot CHBr \cdot CO_2H$ , by treatment with zinc and alcohol. The diiodo compounds are so unstable they immediately break up into iodine and olefine acid.

4. By the elimination of water from hydroxy fatty acids.

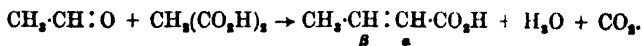


Ethylene-lactic acid

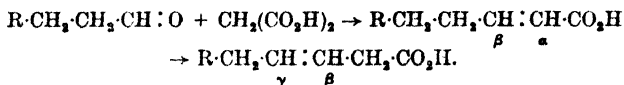
Acrylic acid

This reaction corresponds with the formation of the olefines from monohydric alcohols.

5. By the condensation of an aldehyde with malonic acid in the presence of a tertiary base, e.g. pyridine:



Even with higher aldehydes the product is usually an  $\alpha\beta$ -unsaturated acid when pyridine is used, but with diethylaniline an appreciable amount of the isomeric  $\beta\gamma$ -unsaturated acid is often formed:



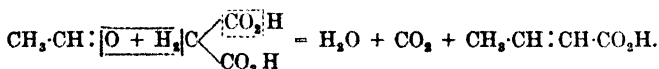
(J. C. S., 1931, 740.)

*Constitution and Isomers.*—The constitution of the unsaturated acids,  $\text{C}_n\text{H}_{2n-2}\text{O}_2$ , follows from their behaviour as monobasic acids and as unsaturated compounds, and the position of the double bond is ascertained by the process of oxidation. The number of isomeric acids,  $\text{C}_m\text{H}_{2m-1}\cdot\text{CO}_2\text{H}$ , is the same as the number of isomeric unsaturated alcohols,  $\text{C}_m\text{H}_{2m-1}\cdot\text{OH}$ .

**Acrylic acid, propene acid, ethylene-carboxylic acid**,  $\text{CH}_2\cdot\text{CH}\cdot\text{CO}_2\text{H}$  (*Redtenbacher*), is prepared by the oxidation of acrolein by oxide of silver, or by the distillation of  $\beta$ -iodopropionic acid with oxide of lead. (Cf. mode of formation 3.) It is very similar to propionic acid. Mixes with water and readily polymerizes. It is reduced to propionic acid when warmed with zinc and sulphuric acid, and is decomposed when fused with alkali into acetic and formic acids.

**Acids,  $\text{C}_4\text{H}_6\text{O}_2$ .** Four isomeric acids with this formula are known. 1. Ordinary or solid crotonic acid (*2-Buten-1-acid*),  $\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ , occurs along with isocrotonic acid in crude pyroligneous acid, and is prepared from allyl iodide by means of the cyanide, which, instead of having the anticipated formula,  $\text{CH}_2\cdot\text{CH}\cdot\text{CH}_2\cdot\text{CN}$ , has the isomeric one,  $\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CN}$ ; this affords another example of molecular transformation.

It is also prepared by heating malonic acid with paraldehyde and glacial acetic acid:



It crystallizes in large prisms, melts at  $72^\circ$ , boils at  $189^\circ$ , has an odour like that of butyric acid, and is fairly soluble in water. On reduction it yields *n*-butyric acid, and on careful oxidation, oxalic acid, hence the constitution.

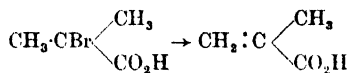
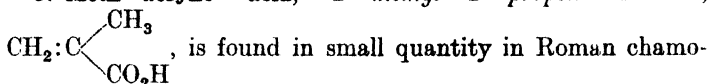
2. **Isocrotonic acid**,  $\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ , obtained by the action of sodium amalgam upon chloro-isocrotonic acid, melts at  $15^\circ$ , boils at  $172^\circ$ , and changes into ordinary crotonic acid



at 180°. It is present in croton-oil. For preparation of the pure acid see *Morrell and Bellars*, J. C. S., 1904, 345.

Isocrotonic acid was formerly regarded as  $\text{CH}_2:\text{CH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , but it shows almost the same chemical behaviour as crotonic acid, e.g. on reduction and oxidation, or on addition of hydrogen bromide, and is now regarded as having the same structural formula as, but being stereo-isomeric with, solid crotonic acid. (Cf. Fumaric and Maleic Acids, Chap. X, B.)

3. **Meth-acrylic acid**, 2-methyl-2-propene-1-acid,



It smells like decaying mushrooms, and melts at 15°.

4. **Vinyl-acetic acid**,  $\text{CH}_2:\text{CH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , 3-Butene-1-acid, may be obtained synthetically.

**Angelic acid**,  $\text{CH}_3\cdot\text{CH}:\text{C}(\text{CH}_3)\text{CO}_2\text{H}$ , is present in the angelica root, and, together with its stereo-isomer, **tiglic acid**, in Roman chamomile oil. The relationship of these two acids is exactly the same as that of crotonic and isocrotonic acids.

**Oleic acid**,  $\text{C}_{18}\text{H}_{34}\text{O}_2$  (*Chevreul*), is present as olein (glyceryl oleate) in the fatty oils especially, e.g. olive, almond, and train oils. It is a colourless oil, solidifies to white needles in the cold, melts at 14°, and cannot be volatilized without decomposition. It is tasteless and odourless, and has no action upon litmus, but quickly becomes yellow and acid by oxidation in the air, and also acquires a rancid odour. Its lead salt is soluble in alcohol or ether, and by this means the acid may be separated from numerous other organic acids. It yields on fusion with potash, the saturated acids, palmitic and acetic. Nitrous acid converts it into the stereo-isomeric crystalline **elaidic acid**, melting at 45°. It contains a normal chain, since on reduction it yields stearic acid. When carefully oxidized, it yields **pelargonic acid**,  $\text{CH}_3\cdot(\text{CH}_2)_7\cdot\text{CO}_2\text{H}$ , and **azelaic acid**,  $\text{CO}_2\text{H}\cdot(\text{CH}_2)_7\cdot\text{CO}_2\text{H}$ , and hence the constitutional formula:  $\text{CH}_3\cdot(\text{CH}_2)_7\cdot\text{CH}:\text{CH}\cdot(\text{CH}_2)_7\cdot\text{CO}_2\text{H}$ . Octadec- $\Delta^9$ -ene-1-acid. Isomers containing the olefine linking in a different position are known, e.g.  $\Delta^2$ -acid.

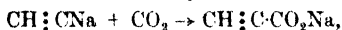
**Erucic acid**,  $C_{22}H_{42}O_2$ , occurs in rape-seed oil, melts at  $33^\circ$ , and on treatment with nitrous acid yields the stereo-isomeric **brassicidic acid**, melting at  $60^\circ$ . The constitution is probably,  $CH_3[CH_2]_7\cdot CH:CH[CH_2]_{11}\cdot CO_2H$ . For the stereo-chemistry of the unsaturated acids see Chap. X, B.

### C. Propiolic Acid Series, $C_nH_{2n-4}O_2$

The acids of this series again contain two atoms of hydrogen less than those of the former, and are to be regarded as carboxylic acids of the acetylene hydrocarbons, e.g. propiolic acid,  $CH:C\cdot CO_2H$ , as acetylene-carboxylic acid. They can accordingly be prepared by the addition of  $CO_2$  to the sodium derivatives of the acetylenes (analogously to mode of formation 4 of the saturated acids, p. 167).

They closely resemble the unsaturated acids which have been already described, but differ from them by the fact that each molecule of such an acid can combine with either 2 or 4 atoms of hydrogen, chlorine, bromine, &c., and can yield explosive compounds with ammoniacal silver and copper solutions. There are, however, acids of the formula  $C_nH_{2n-4}O_2$  which do not possess this last peculiarity, viz. those which are derived not from the homologues of acetylene proper, but from their isomers, and which therefore contain two double bonds instead of a triple one. (Compare Acetylene Hydrocarbons, p. 53.)

The most important member of the series is **propiolic** or **propargylic acid**, *propine acid*,  $CH:C\cdot CO_2H$ , which corresponds with propargyl alcohol, and is prepared by warming an aqueous solution of the acid potassium salt of acetylene-dicarboxylic acid, the latter being itself obtained from dibromo-succinic acid (see Chap. X, A., also B., 1885, 1677), or by the addition of  $CO_2$  to sodium acetylene,



yield 93 per cent. In its physical properties it resembles propionic acid, forms silky crystals below  $18^\circ$ , and boils at  $144^\circ$ . It is readily soluble in water and alcohol, and becomes brown in the air. It gives, even in dilute solution, the characteristic explosive silver precipitate.

**Tetrollic acid**,  $CH_3\cdot C:C\cdot CO_2H$ , is obtained from  $\beta$ -chloro-crotonic acid and aqueous potash, and melts at  $76^\circ$ .

**Sorbic acid**,  $CH_3\cdot CH:CH\cdot CH:CH\cdot CO_2H$ , is contained in

## D. Halogen Substitution Products of the Monobasic Acids

The saturated monobasic acids yield halogen substitution products, e.g.:

Name	Formula	Melting-pt.	Boiling-pt.	$K \times 10^4$
Acetic acid ..	$\text{CH}_3\text{-CO}_2\text{H}$	17°	118°	1.8
Chlor-acetic acid ..	$\text{CH}_2\text{Cl-CO}_2\text{H}$	61	189	155
Dichlor-acetic acid ..	$\text{CHCl}_2\text{-CO}_2\text{H}$	-4	194	5,000
Trichlor-acetic acid ..	$\text{CCl}_3\text{-CO}_2\text{H}$	52	195	30,000
Brom-acetic acid ..	$\text{CH}_2\text{Br-CO}_2\text{H}$	50	208	138
Dibrom-acetic acid ..	$\text{CHBr}_2\text{-CO}_2\text{H}$	48	232	—
Tribrom-acetic acid ..	$\text{CBr}_3\text{-CO}_2\text{H}$	135	dec <sup>a</sup>	—
Iodo-acetic acid ..	$\text{CH}_2\text{I-CO}_2\text{H}$	82	dec <sup>a</sup>	75
Cyano-acetic acid ..	$\text{CN-CH}_2\text{-CO}_2\text{H}$	65	dec <sup>a</sup>	370
Propionic acid ..	$\text{CH}_3\text{-CH}_2\text{-CO}_2\text{H}$	-23	140.7	1.3
$\alpha$ -Chloro-propionic acid	$\text{CH}_3\text{-CHCl-CO}_2\text{H}$	oil	186	147
$\beta$ -Chloro-propionic acid	$\text{CH}_2\text{Cl-CH}_2\text{-CO}_2\text{H}$	41.5	204	8.6
$\gamma$ -Chloro-butyric acid	$\text{CH}_2\text{Cl-(CH}_2)_2\text{-CO}_2\text{H}$	—	—	3
$\alpha$ -Bromo-propionic acid	$\text{CH}_3\text{-CHBr-CO}_2\text{H}$	24.5	203.5	9.8
$\beta$ -Bromo-propionic acid	$\text{CH}_2\text{Br-CH}_2\text{-CO}_2\text{H}$	62.5	—	—
$\alpha$ -Iodo-propionic acid	$\text{CH}_3\text{-CHI-CO}_2\text{H}$	oil	—	—
$\beta$ -Iodo-propionic acid	$\text{CH}_2\text{I-CH}_2\text{-CO}_2\text{H}$	82	—	9
$\alpha$ , $\beta$ -Dibromo-propionic acid	$\text{CH}_2\text{Br-CHBr-CO}_2\text{H}$	64	—	—
$\alpha$ , $\alpha$ -Dibromo-propionic acid	$\text{CH}_3\text{-CBr}_2\text{-CO}_2\text{H}$	61	—	3,300
$\beta$ , $\beta$ -Dibromo-propionic acid	$\text{CHBr}_2\text{-CH}_2\text{-CO}_2\text{H}$	71	—	—

the juice of the unripe sorb apple (*Sorbus Aucuparia*), and has relatively high melting- and boiling-points.

Highly unsaturated normal acids, e.g. **linolic**,  $C_{18}H_{32}O_2$ ,  $\Delta^{9:12}$  diolefine acid, and **linolenic**,  $C_{18}H_{30}O_2$ ,  $\Delta^{9:11:13}$  triolefine acid, occur as glycerides in many oils (Chap. LV, D3).

The unsaturated acids also yield similar substitution products, e.g.  $CH_2:CCl\cdot CO_2H$ ,  $\alpha$ -chlor-acrylic acid;  $CHBr\cdot CH\cdot CO_2H$ ,  $\beta$ -brom-acrylic acid;  $CH_3\cdot CH:CCl\cdot CO_2H$ ,  $\alpha$ -chlor-crotonic acid;  $Cl\cdot C\cdot CO_2H$ , iodo-propionic acid, &c.

All these halogen derivatives have the properties of monobasic acids; in many respects they resemble the parent substances, but as a rule are much stronger acids, particularly with halogen atoms in the  $\alpha$ -position. See value of  $K$  in Table D.

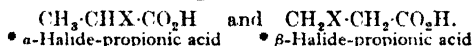
Since their acid nature remains unaltered, they still contain the carboxyl group; the halogen has therefore replaced the hydrogen of the hydrocarbon radical. They may also be regarded as halide substitution products of the hydrocarbons, in which 1 atom of hydrogen is replaced by carboxyl:



The modes of formation and properties of these substituted acids support this view. Thus, as acids they yield salts, esters, chlorides, anhydrides, and amides, and as halides their halogen atoms are exchangeable for OH, CN, or  $SO_3H$ , as are those of the alkyl halides. (See p. 66.)

In the  $\alpha$ -position the halogen is the most reactive, less so with the  $\beta$ - and even less in the  $\gamma$ -position.

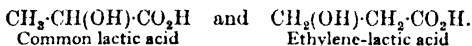
*Isomers and Constitution.*—While in each case only one monodi-, &c., halide acetic acid exists, two isomeric monohalide propionic acids are known. This is readily explicable from the fact that in propionic acid,  $CH_3\cdot CH_2\cdot CO_2H$ , the two  $\alpha$ -hydrogen atoms are differently situated from the three  $\beta$ -ones, the former being attached to the carbon atom nearer to the carboxyl, and the latter to that one farther from it. According to theory, therefore, with which the observed facts agree, the following two isomers are possible:



•  $\alpha$ -Halide-propionic acid      •  $\beta$ -Halide-propionic acid

\* The substituted acids may be termed  $\alpha$ ,  $\beta$ ,  $\gamma$ , &c., or the substituents denoted by numbers. In the latter case the  $\alpha$ -substituted acid is always the 2-substituted, i.e.  $\alpha$ -chloropropionic acid is the 2-chloropropionic acid and the  $\gamma$ -chloro acid is the 3-chloro acid as in the chain of the acid the C of the carboxylic acid is always No. 1.

These acids yield two isomeric lactic acids by exchange of their halogen for hydroxyl, thus:



The constitution of both of these lactic acids follows from their other modes of formation (Chap. IX, A.). The positions of the halogens in the  $\alpha$ - and  $\beta$ -substituted propionic acids are thus also fixed.

Those substituted acids which contain the halogen attached to the  $\alpha$ -carbon atom, i.e. to the same carbon atom to which the carboxyl group is united, are termed  $\alpha$ -acids, and the others  $\beta$ ,  $\gamma$ , &c., acids, the successive carbon atoms in their order from the carboxyl group being designated as  $\alpha$ ,  $\beta$ ,  $\gamma$ , &c.

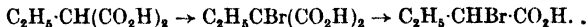
Two stereo-isomeric forms of the  $\alpha$ - or  $\beta$ -mono-chloro- and -bromo-crotonic acids are known (A., 248, 281), being derived from crotonic and isocrotonic acids respectively.

*Formation.*—(a) Of the saturated substituted acids.

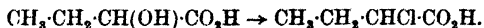
1. Chlorine and bromine can substitute directly, the halogen taking up the  $\alpha$ -position to the carboxyl.

The reaction is often carried out in sunlight and in the presence of a halogen carrier, usually iodine. One of the commonest methods is to transform the acid into the acid bromide by the aid of phosphorus and bromine, and then to brominate. The product obtained, e.g.  $\text{CH}_3\cdot\text{CHBr}\cdot\text{COBr}$ , on treatment with water yields the  $\alpha$ -bromo acid,  $\text{CH}_3\cdot\text{CHBr}\cdot\text{CO}_2\text{H}$ . This is generally known as the *Hell-Volhard-Zelinsky* method. Trimethyl-acetic acid,  $\text{CMe}_3\cdot\text{CO}_2\text{H}$ , which contains no  $\alpha$ -hydrogen atom, cannot be brominated in this manner (B., 1890, 1594) (Chap. LIII, A.).

An  $\alpha$ -bromo substituted fatty acid can be formed by brominating a mono-alkyl substituted malonic acid and subsequent heating when  $\text{CO}_2$  is liberated:



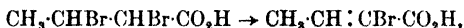
2. From hydroxy acids of the glycollic series by the action of  $\text{PCl}_5$ ,  $\text{HBr}$ , &c., e.g.:



3. By the addition of halogen or halogen hydride to the unsaturated acids. Thus acrylic acid and  $\text{HI}$  yield  $\beta$ -iodo propionic acid.

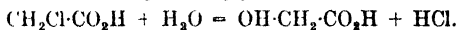
4. An iodo-acid can frequently be obtained by heating a chloro-acid with a solution of potassium iodide.

(b) Of the unsaturated substituted acids. These are often prepared by the elimination of HCl, HBr, or HI from poly-halogen derivatives of the fatty acids by the aid of dilute alkali:



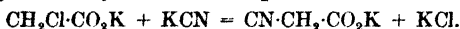
or by the addition of hydrogen halide to propiolic acids.

*Behaviour.*—1. For the replacement of chlorine, bromine, and iodine by hydroxyl, see Chap. IX, A. This exchange takes place with more difficulty in the  $\alpha$ -monochloro-substituted acids than in the corresponding bromine and iodine compounds, but more easily than in the case of the alkyl chlorides, and it is effected by means of moist silver oxide, or frequently by prolonged boiling with water alone (A., 200, 75). In this way, monochloro-acetic yields glycollic acid:



$\beta$ -halogenated acids, on the other hand, lose halogen hydride when boiled with water, and yield unsaturated acids, together with  $\text{CO}_2$  and olefines  $\text{C}_{n-1}\text{H}_{2n-2}$ .  $\gamma$ -halogenated acids break up under these conditions (even with cold soda solution) into HCl, &c., and a lactone, i.e. an anhydride of a  $\gamma$ -hydroxy-acid (Chap. IX, A.; cf. Fittig, A., 208, 116).

2. When boiled with an alcoholic solution of potassium cyanide, cyano-fatty acids\* are produced.



These compounds are on the one hand monobasic acids, and on the other nitriles, and they consequently yield dibasic acids when hydrolysed. In the above case malonic acid,  $\text{CO}_2\text{H-CH}_2\text{-CO}_2\text{H}$ , is formed.

3. They form sulphonic acids with sodium sulphite, e.g.:



These latter compounds are dibasic acids as they contain both  $\text{CO}_2\text{H}$  and  $\text{SO}_3\text{H}$  groups. Their sulpho-group can, however, be replaced by OH on boiling with alkalis.

4. With  $\text{AgNO}_2$ , under favourable conditions, nitro-derivatives of the fatty acids are formed, and these yield amino-acids on reduction, e.g.  $\text{NH}_2\text{-CH}_2\text{-CO}_2\text{H}$  (B., 1910, 3239).

\* These can also be obtained by the addition of HCN to an olefine acid or ester (J. C. S., 1922, 1699).

**Chloroformic acid**,  $\text{Cl}\cdot\text{CO}_2\text{H}$ , has so far not been prepared, although derivatives of it are known. (Cf. Chloro-carbonic acid.)

The chlorinated acetic acids are formed by the direct substitution of acetic acid, or better of acetyl chloride, chlorinated acetyl chlorides ensuing in the latter case as intermediate products.

**Monochlor-acetic acid** (*Chloro-ethane acid*),  $\text{CH}_2\text{Cl}\cdot\text{CO}_2\text{H}$ , is prepared by chlorinating acetic acid, preferably in the presence of acetic anhydride, sulphur, or phosphorus. It forms rhombic prisms or tables and corrodes the epidermis. **Di-chlor-acetic acid**,  $\text{CHCl}_2\cdot\text{CO}_2\text{H}$ , is more conveniently obtained by warming chloral hydrate with potassium cyanide (B., 1877, 2120), and **trichlor-acetic acid**,  $\text{CCl}_3\cdot\text{CO}_2\text{H}$ , by oxidizing chloral hydrate with nitric acid. The former decomposes with boiling alkali to oxalic and acetic acids, and the latter to chloroform and carbon dioxide. Inverse substitution reconverts tri-, di-, and monochlor-acetic acids into acetic acid (*Melsens*, 1842).

**Sulpho-acetic acid**,  $\text{SO}_3\text{H}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , forms deliquescent prisms containing  $1\frac{1}{2}$  mols.  $\text{H}_2\text{O}$  of crystallization. Its salts crystallize well. **Cyano-acetic acid**,  $\text{CN}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , is a crystalline substance melting at  $65^\circ$ – $66^\circ$  and readily soluble in water; it decomposes into aceto-nitrile,  $\text{CH}_3\cdot\text{CN}$ , and  $\text{CO}_2$  when heated, and yields malonic acid on hydrolysis.

**$\alpha$ -Chloropropionic acid**,  $\text{CH}_3\cdot\text{CHCl}\cdot\text{CO}_2\text{H}$ , is obtained by the action of  $\text{PCl}_5$  upon lactic acid, and decomposition of the lactyl chloride,  $\text{CH}_3\cdot\text{CHCl}\cdot\text{COCl}$ , by water. The  $\beta$ -chloro- and bromo-acids are obtained from trimethyleneglycol (Chap. VIII, A.).  **$\beta$ -iodopropionic acid**,  $\text{CH}_2\text{I}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , is prepared by the action of  $\text{PI}_3$  on glyceric acid,  $\text{CH}_2(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$  (exchange of  $2\text{OH}$  for  $2\text{I}$  and of  $\text{I}$  for  $\text{H}$ ; also by acting on acrylic acid with hydriodic acid. It forms colourless six-sided tables of a peculiar odour; m.-pt.  $82^\circ$ . The two **cyanopropionic acids**,  $\text{C}_2\text{H}_4(\text{CN})\cdot\text{CO}_2\text{H}$ , give the two succinic acids when hydrolysed.

**Chloro- and Bromo-crotonic acids**,  **$\beta$ -Chloro-crotonic acid** (*2-Chloro-2-butene acid*) (m.-pt.  $94^\circ$ ) and the stereo-isomeric  **$\beta$ -Isochloro-crotonic acid** (m.-pt.  $59.5^\circ$ ) are formed by the action of  $\text{PCl}_5$  on ethyl acetoacetate, and treatment of the product with water. The  $\beta$ -chloro-iso-acid volatilizes with steam, but the  $\beta$ -chloro-acid does not.

## VII. ACID DERIVATIVES

A general idea of the types of derivatives to which acids give rise is obtained by comparing these derivatives with corresponding derivatives of the saturated monohydric alcohols, e.g. those of acetic acid with those derived from ethyl alcohol:

$\text{CH}_3\cdot\text{CH}_2\cdot\text{OH}$	Alcohol.	$\text{CH}_3\cdot\text{CO}\cdot\text{OH}$	Acetic acid.
$\text{CH}_3\cdot\text{CH}_2\cdot\text{ONa}$	Sodium ethoxide.	$\text{CH}_3\cdot\text{CO}\cdot\text{ONa}$	Sodium acetate.
$\text{CH}_3\cdot\text{CH}_2\cdot\text{O}$	Ethyl ether.	$\text{CH}_3\cdot\text{CO}\cdot\text{O}$	Ethyl acetate.
$\text{CH}_3\cdot\text{CH}_2\cdot\text{O}$		$\text{CH}_3\cdot\text{CH}_2\cdot\text{O}$	
$\text{CH}_3\cdot\text{CH}_2\cdot\text{Cl}$	Ethyl chloride.	$(\text{CH}_3\cdot\text{CO})_2\text{O}$	Acetic anhydride.
$\text{CH}_3\cdot\text{CH}_2\cdot\text{SH}$	Mercaptan.	$\text{CH}_3\cdot\text{CO}\cdot\text{Cl}$	Acetyl chloride.
$\text{CH}_3\cdot\text{CH}_2\cdot\text{NH}_2$	Ethylamine.	$\text{CH}_3\cdot\text{CO}\cdot\text{SH}$	Thiacetic Acid.
		$\text{CH}_3\cdot\text{CO}\cdot\text{NH}_2$	Acetamide.

It is seen that as regards formulæ there is a close resemblance, the acetyl group taking the place of the ethyl group. Stated generally, the acid derivatives contain acyl radicals in place of the alkyl groups contained in the corresponding derivatives of alcohols.

These derivatives are obtained by methods many of which are perfectly analogous to the modes of formation of the corresponding alkyl derivatives, but they differ characteristically from these by being less stable towards hydrolysing agents.

A number of other derivatives, viz. amido- and imido-chlorides, thiamides, imido-thio-compounds, and amidines, are peculiar to the acids:

$\text{CH}_3\cdot\text{CCl}_2\cdot\text{NHR}^*$	Amido-chlorides.	$\text{CH}_3\cdot\text{C}(\text{OH})\cdot\text{NH}$	Imino-compounds.
$\text{CH}_3\cdot\text{CCl}\cdot\text{NR}$	Imido-chlorides.	$\text{CH}_3\cdot\text{C}(\text{SH})\cdot\text{NH}$	Imino-thio- „
$\text{CH}_3\cdot\text{CS}\cdot\text{NH}_2$	Thiamides.	$\text{CH}_3\cdot\text{C}(\text{NH}_2)_2\cdot\text{NH}$	Amidines.

These compounds are also characterized by being readily hydrolysed.

## A. Esters of the Fatty Acids

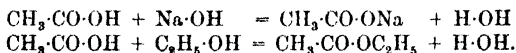
Mineral acids readily give rise to esters by the replacement of their acidic hydrogen radicals by alkyl groups, e.g.  $\text{SO}_2(\text{OH})_2 \rightarrow \text{SO}_2(\text{OEt})_2$  (Chap. IV, C.). In exactly the same manner

\* R signifies an alkyl or aryl radical.



by replacing the typical hydrogen of the fatty acids by alkyl groups, esters derived from the fatty acids, e.g. ethyl acetate,  $\text{CH}_3\cdot\text{CO}_2\text{Et}$ , are obtained. Since these esters correspond with the metallic salts, they are sometimes termed alkyl salts. (Cf.  $\text{CH}_3\cdot\text{CO}_2\text{K}$  and  $\text{CH}_3\cdot\text{CO}_2\text{Et}$ ).

*Methods of Formation.*—1. By direct esterification, i.e. by direct action of the acid on the alcohol:

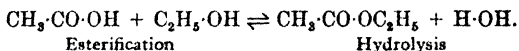


Although the equation representing the reaction is analogous to that representing the neutralization of acetic acid by an alkali, the process of esterification differs from that of neutralization in three respects.

(1) The reaction proceeds but slowly; thus, in the esterification of acetic acid by ethyl alcohol the limit of the reaction at the boiling-point is not reached until after the lapse of several hours, and even then only two-thirds of the acid have been transformed into ester.

(2) In the equation  $k = Be^{-E/RT}$ , when the reaction is instantaneous as in neutralization  $E$  the energy of activation is zero, but in other cases as in esterification,  $E$  has a definite value, for esterification 10,200 gm. cal.

(3) The reaction is a reversible or balanced one, and hence is never complete. The water which is formed during the process of esterification tends to hydrolyse the ester back into acid and alcohol:



Thus, when equivalent quantities of acetic acid and ethyl alcohol are employed, only some 66 per cent of the acid becomes transformed into ester. It can readily be shown, by aid of *Guldberg* and *Waage's* law of mass action, that by employing an excess of alcohol a larger proportion of acid will be converted into ester. Thus, in the above equation, if the original concentrations of the four substances expressed in gram molecules be denoted by  $a$ ,  $b$ , 0 and 0, and the velocity constants of the direct and reverse reactions by  $k_1$  and  $k_2$  respectively, then after time  $t$  equilibrium will be established; and if  $x$  gram molecules of acid have been esterified, then the concentrations of the four substances will be  $a - x$ ,  $b - x$ ,  $x$  and  $x$ .

The rate of the direct reaction can be denoted by  $k_1(a-x)(b-x)$ , and that of the reverse by  $k_2x^2$  (*Guldberg and Waage*). When equilibrium is established, the two reactions will proceed at the same rate, and

$$k_1(a-x)(b-x) = k_2x^2,$$

or  $\frac{(a-x)(b-x)}{x^2} = \text{constant for a given temperature.}$

In the case of acetic acid and ethyl alcohol, using gram molecular proportions, i.e.  $a = b = 1$ , equilibrium is established when some two-thirds of acid are esterified. Thus

$$\frac{(1 - \frac{2}{3})(1 - \frac{2}{3})}{(\frac{2}{3})^2} = \text{constant},$$

and the constant becomes equal to  $\frac{1}{4}$ .

By using 2 gm. molecules of alcohol to 1 of acid the equation is:

$$\frac{(1-x)(2-x)}{x^2} = \frac{1}{4}.$$

$$x = .85 \text{ (approx.)},$$

and thus 85 per cent of the acid will have been esterified in place of the 66 per cent when only 1 gm. mol. of alcohol was used. The reversible nature of the reaction is of especial importance in the preparation of ethyl acetate, and in this case the difficulty is overcome by the addition of a moderate amount of concentrated sulphuric acid, which is ordinarily supposed to react with the water, and thus prevent its hydrolysing the ester. (Compare also *Wade*, J. C. S., 1905, 1656.)

It is worthy of note that the limit of esterification does not vary to any large extent with the temperature. Thus, in the case mentioned above, the limit at  $10^\circ$  is 65.2 per cent, and at  $220^\circ$  it is only 66.5 per cent.

In order to increase the limit without using a large excess of alcohol, several methods for removing the water as it is formed have been adopted. One of these is to distil over the water and excess of alcohol into anhydrous  $K_2CO_3$ , which combines with the water, and then to distil the alcohol back on to the acid. (J. C. S., 1929, 1707.)

Another method is to form a ternary mixture of low boiling-point by adding a suitable solvent and by distillation removing the water (Org. Syn., 1922, 23; 1930, 88).

With most of the higher esters and more especially the esters in the aromatic series, the limit of esterification is much higher, as the esters are not so readily hydrolysed. In these cases, however, the rates at which the esters are formed are extremely slow, and a catalytic agent is therefore introduced. The two common catalytic agents employed are: (1) A small amount of dry hydrogen chloride. At one time it was customary to saturate the boiling alcoholic solution of the acid with hydrogen chloride, but the researches of *E. Fischer* and *Speier* (B., 1895, 3201, 3252) have shown that the addition of 3 per cent of dry hydrogen chloride to the alcoholic solution is quite sufficient. (2) A small amount of concentrated sulphuric acid, which acts in much the same manner as the hydrogen chloride. These reagents do not raise the limit of esterification, but accelerate the production. In most cases using the catalytic method at the boiling-point of the alcohol, the reaction is complete after three hours, and a 90–95 per cent yield of ester can be obtained by pouring into water.

A number of researches have been made as to the influence of the constitution of the acid and of the alcohol on the rate of esterification, i.e. the amount of ester formed in unit time. *Menschutkin*, who employed the direct esterification method without a catalytic agent, i.e. the so-called auto-catalytic method, found that primary acids, i.e.  $R \cdot CH_2 \cdot CO_2H$ , were esterified most quickly; secondary acids,  $RR'CH \cdot CO_2H$ , were intermediate; and tertiary acids,  $RR'R''C \cdot CO_2H$ , least readily when the same alcohol was employed. Other researches tend to show that in the absence of a catalyst strong acids react with alcohol more readily than feeble acids; thus trichloroacetic acid is esterified more rapidly than acetic acid.

The process of catalytic esterification readily lends itself to study as a time reaction. By using a large excess of the alcohol and a known concentration of catalyst, the reaction should be one of the first order—a unimolecular reaction—and hence the equation  $k = (1/t) \log\{a/(a-x)\}$ , where  $t$  is the time,  $a$  the concentration of the acid at the beginning, and  $a-x$  the concentration after time  $t$ .

It is found that the values of  $k$  tend to diminish as  $t$  increases, due to the inhibiting action of the water formed on the catalyst and *Goldschmidt* and *Udby* (Z. phys., 1907, 60, 728) have introduced a modified formula  $k = (1/t)(r+a) \log\{a/(a-x)\}$ , where  $r$  is a constant 0.15 for ethyl alcohol.

By determining the relative rates of esterification of fatty acids with the same alcohol it has been shown that the presence of any substituent in the acetic acid molecules tends to retard esterification. (Cf. Chap. XXXVI, Steric Effects, Steric Hindrance.)

The influence of the hydrogen chloride is purely catalytic; it remains unchanged at the end of the reaction. Its catalysing effect is partly due to the hydrions it generates, as strong acids (HCl, HBr) are much better catalysing agents than weaker acids (picric acid), but also to the undissociated molecules. (Cf. *Goldschmidt*, B., 1895, **28**, 3218; *Z. elect.*, 1911, **17**, 684; *Snethlage*, *Zeit. phys.*, 1915, **90**, 142.

Ultra-violet light accelerates the reaction between organic acids and alcohols (B., 1914, 1803).

2. By the action of an acid chloride upon an alcohol or its sodium compound (Chap. VII, B.).



3. By the action of alkyl halides upon salts of the acid:



Individual acids are often characterized by forming their *p*-nitrobenzyl esters by the action of *p*-nitrobenzyl bromide,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{Br}$  on the sodium salt of the acid (*Reid*, J. A. C. S., 1917, 124).

As a rule, an alkyl iodide and the silver salt of the acid are employed. The ester can then be separated from the solid silver iodide and distilled. Occasionally the potassium salt and methyl sulphate are used. Reactions 2 and 3 are of very general application, and are largely made use of when an ester cannot readily be obtained by the catalytic method of esterification.

4. Esters may also be made catalytically in the vapour phase from the acid and alcohol with a metallic oxide at 280–300° (cf. Chap. XLIX, E.).

A modification is the direct formation from an olefine and acetic acid in the vapour phase at 110° using carbon activated by phosphoric acid as catalyst, e.g. propylene and acetic acid yield *iso*-propyl acetate.

5. Certain esters are formed from aldehydes by the action of aluminium ethoxide; cf. p. 88; e.g. ethyl acetate from

acetaldehyde with aluminium ethoxide and zinc chloride in ethyl alcoholic solution.

6. Primary alcohols yield esters, e.g. butyl alcohol gives butyl butyrate and ethyl alcohol ethyl acetate when the alcohol vapour is passed over a complex catalyst containing U, Ba, Ag, Cu and Al at 250-400° and 200 atm. pressure. Probably an aldehyde is first formed by dehydrogenation and this yields the ester.

*Properties.*—The esters are mostly neutral liquids which volatilize without decomposition; only those which contain a small number of carbon atoms in the molecule are soluble in water, e.g. ethyl acetate (1 : 14).

1. **Hydrolysis.**—They are all hydrolysed (saponified), i.e. resolved back into alcohol and acid, when heated, or better, superheated, with water, or when boiled with aqueous solutions of strong alkalis or mineral acids; with some esters this hydrolysis is complete when the ester is allowed to remain for some time in contact with water or dilute alkali.

The hydrolysis of an ester under the influence of water or of mineral acids may be represented by the equation:



and may be studied by the aid of the general equation for a uni-molecular reaction,  $k = \frac{1}{t} \log \frac{a}{a-x}$ , since the concentration of the water, if a large excess is used, may be regarded as constant.

The action of the mineral acid is purely catalytic. The same result might ultimately be obtained by using water alone, but is considerably accelerated by using a small amount of a strong mineral acid (HCl, H<sub>2</sub>SO<sub>4</sub>). Weak acids also accelerate the hydrolysis of the ester, but to a less extent. It has been found, using the same ester and equivalent quantities of different acids, that the rate of hydrolysis is directly proportional to the strength of the acid. In other words, the catalysing influence of different acids is due to the hydriions.

The hydrolysis of an ester by alkalis is represented by the equation:  $R \cdot CO \cdot OR' + NaOH = R \cdot CO \cdot ONa + R' \cdot OH$ , and as it is analogous to the preparation of soaps by the action of alkalis on fats (p. 184), is commonly termed Saponification. This is a bimolecular reaction, and if equivalent quantities of ester and alkali are employed in solution, can be studied by

aid of the equation  $k = \frac{1}{t} \cdot \frac{x}{a(a-x)}$ , where  $t$  = time,  $a$  = initial concentration of alkali and of ester,  $a - x$  = concentration of these after time  $t$ . The concentrations can readily be determined by direct titration with standard acid.

It has been found that when different alkalis are employed, their hydrolysing effect is proportional to their strengths, i.e. is due to the free hydroxyl ions. Different esters are hydrolysed at very different rates by the same alkali; the rate appears to depend on the complexity of the molecule, i.e. the number of substituents present, and also on the nature of these substituents, viz. whether they are of a positive or negative nature. It has been found that  $\text{CCl}_3 \cdot \text{CO}_2 \text{C}_2\text{H}_5$  is hydrolysed by alcoholic potash much more readily than ethyl acetate itself, owing to the negative nature of the chlorine substituents. (Compare A., 228, 257; 232, 103; J. C. S., 1899, 482.)

In all cases it has been found that, comparing solutions of equal strength, e.g. N/10, a strong alkali is a much better hydrolysing agent than a strong acid.

2. A characteristic reaction of methyl and ethyl esters is that they exchange OMe (**methoxy**) or OEt (**ethoxy**) groups for  $\text{NH}_2$  on treatment with strong ammonia, thus yielding acid amides, e.g.  $\text{CH}_3 \cdot \text{CO} \cdot \text{NH}_2$ .

3. Phosphorus pentachloride decomposes most esters, yielding an alkyl chloride and an acyl chloride, the O of the OEt group being replaced by two chlorine atoms.

4. Ethyl esters are readily transformed into methyl esters,  $\text{R} \cdot \text{CO}_2 \text{Et} \rightarrow \text{R} \cdot \text{CO}_2 \text{Me}$ , by warming with methyl alcohol and a catalyst ( $\text{CH}_3\text{ONa}$ ,  $\text{HCl}$ ). The reaction is reversible, holds good for other alcohols, and is termed **alcoholysis**.

5. Esters react with *Grignard* compounds forming tertiary alcohols (Chap. IV, H.).

6. They can be reduced to primary alcohols by sodium and boiling ethyl or amyl alcohol (*Bouveault* and *Blaise*).

7. Sodium methoxide combines with the esters to form unstable additive compounds,  $\text{R} \cdot \text{C} \begin{array}{l} \nearrow \text{ONa} \\ \searrow \text{OCH}_3 \\ \text{OR}' \end{array}$ , which are derivatives

of "ortho-acids". (See p. 166; also B., 1887, 646.)

The odour and taste of many of the esters are so agreeable that they are manufactured upon a large scale, and employed as fruit essences.

**Ethyl formate**,  $\text{H}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , b.-pt.  $55^\circ$ , is employed in the manufacture of artificial rum or arrak. **Ethyl acetate**, *acetic ether*,  $\text{CH}_3\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , b.-pt.  $75^\circ$ , is used internally as a medicine. **Amyl acetate**,  $\text{CH}_3\cdot\text{CO}\cdot\text{OC}_5\text{H}_{11}$ , b.-pt.  $148^\circ$ . The alcoholic solution of this forms the essence of pears. **Ethyl butyrate**,  $\text{CH}_3(\text{CH}_2)_2\text{CO}\cdot\text{OC}_2\text{H}_5$ , is the essence of pine-apples. **Iso-amyl iso-valerate**,  $\text{C}_4\text{H}_9\cdot\text{CO}\cdot\text{OC}_5\text{H}_{11}$ , b.-pt.  $196^\circ$ , finds application as apple oil or apple ether. **Cetyl palmitate**,  $\text{C}_{15}\text{H}_{31}\cdot\text{CO}\cdot\text{OC}_{16}\text{H}_{33}$ , **ceryl cerotate**,  $\text{C}_{25}\text{H}_{51}\cdot\text{CO}\cdot\text{OC}_{26}\text{H}_{53}$ , and **melissic palmitate**,  $\text{C}_{15}\text{H}_{31}\cdot\text{CO}\cdot\text{OC}_{30}\text{H}_{61}$ , are constituents of waxes. (See Wax Varieties, p. 183.)

Ethyl acetate, which is used as a solvent and also for the preparation of ethyl aceto-acetate (Chap. IX, H), is usually prepared from alcohol, acetic acid, and an excess of sulphuric acid. Another method consists in passing aldehyde (prepared from acetylene) into a solution of aluminium ethoxide,  $\text{Al}(\text{OEt})_3$ , in a high-boiling solvent. The yield is 85 per cent of the theoretical and the consumption of aluminium ethoxide is only 3–5 per cent (C. Z., 1918, ii, 693).

Continuous methods are often employed. (1) Making use of an azeotrope. It is necessary to add more ethyl acetate with the alcohol and acid as the azeotrope contains less water than is formed in the reaction and in this way all the water distils over with the ester.

(2) By passing a mixture of alcohol and acid with 3 per cent of sulphuric acid down the lower portion of a fractionating column, the ester mixture passes up the column and ethyl acetate with some alcohol passes into the receiver.

Although the reaction between alcohol and acetic acid is a balanced one and the water formed tends to decompose the ester, *Bodroux* (C. R., 1913, **156**, 1079; 1914, **157**, 938) has shown that a 92 per cent yield of ethyl acetate is formed when a mixture of acetic acid and alcohol is boiled with a 10 per cent aqueous solution of sulphuric acid, and the ester removed by distillation as fast as it is formed. Equally good results can be obtained with esters derived from other fatty acids and primary alcohols, provided the esters boil below  $100^\circ$ .

Esters of the higher acids when distilled under atmospheric pressure decompose into an olefine and a fatty acid. (See p. 49.)

*n*-Butyl acetate and iso-amyl acetate are manufactured for solvents for nitrocellulose paints and varnishes.

*Isomers*.—All esters containing the same number of C atoms

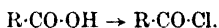
in the molecule, and derived from the monohydric saturated alcohols and the fatty acids, are isomeric. Thus methyl butyrate is isomeric not only with ethyl propionate but also with propyl acetate and with butyl formate. Further, all esters are isomeric with the monobasic acids which contain an equal number of carbon atoms, e.g. the esters just mentioned are isomeric with the valeric acids.

Further cases of isomerism occur when the alcohol on the one hand, or the acid on the other, is unsaturated, e.g. allyl propionate and propyl acrylate.

Particular esters are often detected by conversion into their corresponding anilides by treatment with anilino-magnesium bromide,  $C_6H_5 \cdot NH \cdot MgBr$ , from aniline and  $EtMgBr$ . (*Hardy*, J. C. S., 1936, 198.)

## B. Acid or Acyl Chlorides, Bromides, &c.

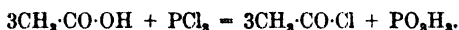
Acyl chlorides are the compounds derived from the acids by the replacement of the hydroxyl group by chlorine:



1. They are usually prepared by the action of the chlorides of phosphorus,  $PCl_3$ ,  $PCl_5$ , upon the acids.



The acid chloride is separated from the  $POCl_3$  formed at the same time by fractional distillation. In the case of acetic acid  $PCl_3$  is conveniently used:



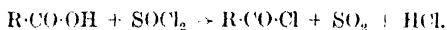
A recent process is the action of  $PCl_3$  on a mixture of acid and acid anhydride. No  $HCl$  is evolved, and an 85 per cent yield of acid chloride is obtained. E.P., 26140 of 15, iii, 1926.

Phosphorus oxychloride,  $POCl_3$ , reacts with the alkali salts of the acids; the products are the acid chloride, and an alkali chloride and metaphosphate. When an alkali salt is used, an acid anhydride is formed in the absence of excess of the phosphorus halide (Section C., below).

Thionyl chloride is very frequently used in place of chlorides



of phosphorus as the acid chloride is readily isolated (*M' Master and Ahmann*, J. A. C. S., 1928, 145).



2. By the action of chlorine upon the aldehydes in the absence of water:  $CH_3\cdot CHO + Cl_2 = CH_3\cdot COCl + HCl$ .

The bromides and iodides can be obtained by the action of  $HBr$  or  $HI$  on the chlorides.

*Properties.*—The acid chlorides are suffocating liquids which fume in the air, distil without decomposition, and are reconverted by water, in many cases at the ordinary temperature, into the corresponding acids and hydrochloric acid:

They are thus more readily decomposed than the alkyl chlorides. When the chlorides are warmed with alcohols, the chlorine is replaced by alkyloxy groups, e.g.  $OCH_3$ ,  $OC_2H_5$ , and in this way esters are formed. With ammonia they yield acid amides,  $R\cdot CO\cdot NH_2$ . With the sodium salts of the fatty acids they yield acid anhydrides. With organo-magnesium compound they first form ketones, and then tertiary alcohols (pp. 80 and 141). With silver cyanide acyl cyanides (e.g.  $CH_3\cdot CO\cdot CN$ , acetyl cyanide) are formed, and these on hydrolysis with concentrated hydrochloric acid yield ketonic acids,  $CH_3\cdot CO\cdot COOH$ .

The acid chlorides can be regarded as aldehydes in which the hydrogen atom of the  $\cdot CH:O$  group has been replaced by chlorine. As such they can be reduced to the aldehydes, and the most convenient method appears to consist in passing a current of hydrogen into a hot xylene solution of the chloride containing palladinized barium sulphate in suspension as catalyst. (*Rosemund*, B., 1918, 585; 1922, 2357, 2888.)

Formyl chloride is not known.

**Acetyl chloride** (*Ethanoyl chloride*),  $CH_3\cdot COCl$ , is a mobile, colourless liquid of suffocating odour. Boils at  $55^\circ$ , has a sp. gr. 1.13 at  $0^\circ$ , reacts extremely vigorously with water and ammonium hydroxide, and is a reagent of exceptional importance, since it serves for the conversion of the alcohols and primary and secondary amines into their acetyl derivatives. It is thus frequently used for detecting  $OH$ ,  $NH_2$  or  $NH$  groups in organic compounds. The compound under examination is heated with acetyl chloride (or even better, acetic

anhydride), and the pure product either analysed or hydrolysed, and acetic acid tested for in the products of hydrolysis (cf. Chap. VIII, C.).

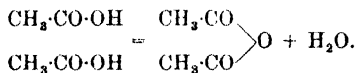
With hydroxyl compounds the H of the OH becomes replaced by the acetyl group and a compound  $R \cdot O \cdot CO \cdot CH_3$ , viz. an alkyl acetate is formed.

When several hydroxyl groups are present in a molecule, as in glycerol, it frequently happens that most of these become replaced by acetoxy and one by chlorine. For complete acetylation acetic anhydride is preferable.

Acid bromides and iodides closely resemble the chlorides. Their boiling-points are higher.

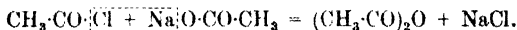
### C. Acid Anhydrides

Corresponding with the monobasic fatty acids there are anhydrides, which may be regarded as derived from two molecules of the acid by the elimination of a molecule of water, e.g.:



They may also be considered as **acyl oxides**. For instance,  $(CH_3 \cdot CO)_2O$  = **acetyl oxide**.

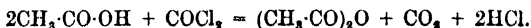
*Preparation.*—1. They can be obtained by the direct withdrawal of water from the acids, e.g. by passing the acid over silica gel with or without another catalyst at  $550-600^\circ$  or over fused phosphate in graphite containers. 2. By the action of acid chlorides upon the alkali salts of the acids:



A very convenient method for preparing them is by the action of phosphorus oxychloride on the sodium salts of the acids, care being taken that sufficient of the dry sodium salt is used to decompose the acid chloride first formed (see p. 205).

Thionyl chloride can be used instead of  $POCl_3$ , an intermediate product,  $(R \cdot CO \cdot O)_2SO$ , is formed, and this breaks up into  $SO_2$  and  $(R \cdot CO)_2O$  when heated, or with excess of  $SOCl_2$  it yields  $SO_2$  and  $R \cdot COCl$ . (*Denham and Woodhouse*, J. C. S., 1913, 1861.)

3. By the action of phosgene on the acids (B., 1884, 1286):

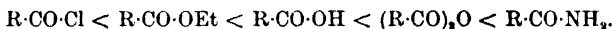


4. The anhydrides of the higher acids are often prepared by the action of acetic anhydride on their sodium salts.

*Properties.*—The majority of the acid anhydrides are liquids, but those of higher molecular weight solids of neutral reaction, and soluble in alcohol and ether. They are non-miscible with water, but are gradually hydrolysed by it to the free acids. Dilute alkalis decompose them readily. When warmed with alcohols they yield esters; with ammonia, acid amides; and with hydrogen chloride, free acid and acid chloride:



The boiling-points follow the order:



Compare analogous alkyl compounds.

**Acetic anhydride**  $(\text{CH}_3\cdot\text{CO})_2\text{O}$ , is a mobile liquid of suffocating odour, boiling at  $137^\circ$ , and having a sp. gr. of 1.073 at  $20^\circ$ . Like acetyl chloride it is a reagent of great importance, and is largely made use of in testing for and estimating hydroxyl groups in carbon compounds, and for converting hydroxy-, amino-, and imino-compounds into acetyl derivatives, e.g. for manufacturing acetylcellulose for artificial silk. A catalytic method of manufacture consists in passing dry acetic acid vapour over dry BaO or ZnO at  $250^\circ$ – $300^\circ$  and fractionating the product.

In preparing acetyl derivatives by means of the anhydride a small amount of a catalyst, e.g. concentrated sulphuric acid is frequently used.

**Mixed anhydrides** containing two different acyl groups are also known (*Gerhardt, Williamson*), e.g.  $\text{C}_2\text{H}_5\text{O}\cdot\text{O}\cdot\text{OC}_5\text{H}_{11}$ . When distilled they yield the two simple anhydrides.

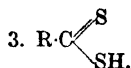
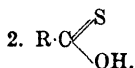
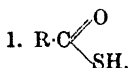
Acyl peroxides have also been prepared. **Acetyl peroxide**,  $(\text{C}_2\text{H}_5\text{O})_2\text{O}_2$ , is a thick liquid insoluble in water; it acts as a strong oxidizing agent, explodes when heated, and is prepared by the action of barium peroxide,  $\text{BaO}_2$ , upon acetic anhydride. Numerous other **peroxides** have been prepared by *Baeyer and Villiger* (B., 1901, 738) by means of hydrogen peroxide in the presence of potassium hydroxide. Among the simpler

of these peroxides may be mentioned **ethyl hydrogen peroxide**,  $C_2H_5 \cdot O \cdot O \cdot H$ , a colourless liquid; **diethyl peroxide**,  $C_2H_5 \cdot O \cdot O \cdot C_2H_5$ , a liquid boiling at  $65^\circ$ ; **acetone peroxide**,  $(C_3H_6O_2)_2$ , boiling at  $132^\circ$ ; and **triacetone peroxide**,  $(C_3H_6O_2)_3$ , melting at  $97^\circ$ . Many of these compounds are explosive.

Such peroxides are formed by (1) The alkylation of hydrogen peroxide. (2) Treatment of alcohols, ethers, olefines, aldehydes, acids, &c., with oxygen, ozone or perhydrol. (3) Decomposition of ozonides (Chap. XLVIII, G.).

## D. Thio-acids and Thio-anhydrides

The sulphur analogues of the carboxylic acids are:

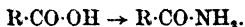


Known respectively as thiolic, thionic, and thion-thiolic acids.

**Thiacetic acid** (*Ethane-thiolic acid*),  $CH_3 \cdot CO \cdot SH$ , is a colourless liquid boiling below  $100^\circ$ ; it smells of acetic acid and sulphuretted hydrogen, and is readily decomposed by water into these two components. It is prepared from acetic acid and phosphorus pentasulphide,  $P_2S_5$ . The other thio-compounds are also readily hydrolysed, yielding acetic acid and hydrogen sulphide.

## E. Acid Amides and Hydrazides

**Amides.**—An acid amide is the compound derived from the acid by the introduction of the amido\* group in place of the hydroxyl radical of the carboxylic group:

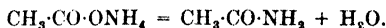


They may also be regarded as derived from ammonia by the replacement of a hydrogen atom by an acyl group, e.g.  $NH_2 \cdot CO \cdot CH_3$ . **Secondary and tertiary amides**, e.g.  $NH(CO \cdot CH_3)_2$ ,

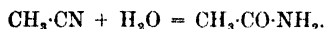
\* The  $NH_2$  group is usually termed an amino group when present in a primary amine, but an amido group when present in an acid amide.

and  $\text{N}(\text{CO}\cdot\text{CH}_3)_3$ , are known, but are of relatively small importance.

*Modes of Formation.*—1. By the dry distillation of the ammonium salts of the fatty acids:

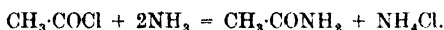


2. By addition of water to the alkyl cyanides (nitriles):

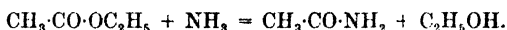


This addition of water is frequently effected by dissolving the nitrile in concentrated sulphuric acid, or in acetic and concentrated sulphuric acids, or by shaking with concentrated hydrochloric acid in the cold; also, and often quantitatively, by hydrogen peroxide,  $\text{H}_2\text{O}_2$ , in alkaline solution. In some cases a further addition of water occurs, and the ammonium salt of the acid is formed.

3. By the action of acid chlorides or acid anhydrides upon aqueous ammonia or solid ammonium carbonate; if amines are employed, in place of ammonia, **alkylated amides** are formed:



4. By heating esters with ammonia solution, sometimes even on shaking in the cold:



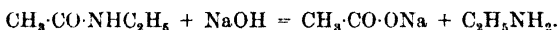
*Properties.*—1. With the exception of formamide they are colourless crystalline compounds, volatile without decomposition, but with relatively high boiling-points. The following comparison of boiling-points is interesting, as the order is the same for most groups:

	Acetyl chloride	Ethyl acetate	Acetic acid	Acetic anhydride	Acetamide
Boiling-points	55°	78°	117°	137°	220°

2. The lower members are soluble in water, and although derivatives of ammonia, are, unlike most amines, practically neutral, the strongly positive character of the hydrogen atoms of the ammonia being cancelled by the entrance of the negative acyl radical. Still, the primary amides are capable of forming additive compounds with some acids, e.g. acetamide yields the compound  $(\text{C}_2\text{H}_3\text{O}\cdot\text{NH}_2)_2\text{HCl}$ , "**acetamide hydrochloride**"; these are, however, unstable, and are decomposed

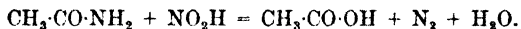
for the most part by water alone. On the other hand, the hydrogen of the amido group can be replaced by particular metals, especially mercury (or sodium by the action of the metal or of sodamide), the salts probably having the structure  $R \cdot C(ONa) : NH$ . The formation of such sodium salts is of value in the preparation of primary and secondary amines; cf. B., 1890, 3037; 1895, 2353), the amides, therefore, playing the part of weak acids in the compounds so obtained, e.g. **mercury acetamide**,  $(CH_3 \cdot CONH)_2Hg$ .

3. **Hydrolysis of Acid Amides.**—The amides are readily hydrolysed, more especially by alkalis, to the free acid and ammonia. Alkylated amides on hydrolysis yield the acid (or sodium salt) and an amine (not ammonia). Amines are not decomposed by alkalis.



The velocity of hydrolysis of the amides of the common fatty acids has been determined by *Crocker and Lowe* (J. C. S., 1907, 593 and 952), using an electro-conductivity method. With sodium hydroxide and also hydrochloric acid, formamide is hydrolysed most readily, and valeramide least readily.

4. Nitrous acid converts the primary amides into the corresponding acids, with liberation of nitrogen:

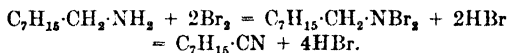


This reaction is a general one, and corresponds exactly with the action of nitrous acid upon the primary amines (p. 119).

5. Nitriles (see p. 111) are formed by heating with  $P_4O_{10}$ ,  $P_2S_5$ , and  $PCl_5$  (see p. 214).

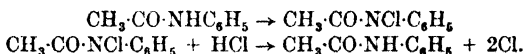
6. If bromine in the presence of alkali is allowed to act upon primary amides, bromamides,  $R \cdot CO \cdot NHBr$ , e.g.  $CH_3 \cdot CO \cdot NHBr$ , **aceto-bromamide** (colourless rectangular plates), are first formed, and these are decomposed by the alkali into a primary amine, carbon dioxide and potassium hydroxide. If less bromine is used, urea derivatives are formed, e.g. methyl acetyl-urea,  $CH_3 \cdot NH \cdot CO \cdot NH \cdot CO \cdot CH_3$ , which react with excess of alkali, yielding primary amines—in this case  $CH_3 \cdot NH_2$ —containing 1 atom of carbon less than the original amide. This is an excellent method for the preparation of amines from  $C_1$  to  $C_5$ , but less valuable for those from  $C_6$  onwards, as in the case of the higher compounds the production of amine diminishes, a nitrile being formed instead by the further action

of the bromine (see below). Such nitriles  $C_nH_{2n+1}\cdot CN$ , in which  $n > 4$ , can therefore be obtained directly from the amine by the action of bromine and alkali upon it, thus:

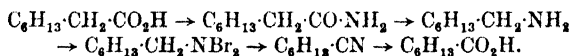


(Reversal of the *Mendius* reaction, p. 117; cf. *Hofmann*, B., 1882, 407, 752; 1884, 1407, 1920; 1885, 2737.)

The N-chloro derivative of alkylated amides are of value as chlorinating agents when excess of Cl is deleterious as by the gradual addition of hydrochloric acid chlorine can be liberated gradually:

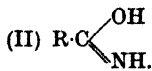
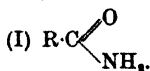


Since these nitriles on hydrolysis yield acids containing one atom of carbon less than the amide originally taken, this reaction renders it possible to descend in the series successively from one acid to another (compare p. 185), e.g.:



This has been done in the case of the normal acids from  $C_{14}$  to  $C_1$ , and it furnishes a further proof of their normal constitution.

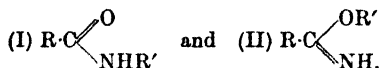
*Constitution.*—Most of the methods of formation and many of the properties of the amides point to the constitutional formula (I). A second formula is possible (II), in favour of which certain arguments have been adduced (B., 1889, 3273; 1890, 103; 1892, 1435):



This last formula easily passes into the first by the migration of a hydrogen atom, and most of the reactions of the simple amides are explicable almost equally well by either formula. (Cf. *Titherley*, J. C. S., 1897, 468; 1901, 407.)

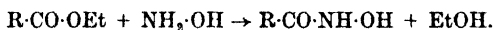
Thus a single compound appears to possess, according to its reactions, two distinct formulae. Such a substance is usually termed a **tautomeric substance** (Chap. LIII).

On alkylation, under different conditions, it is possible to obtain two distinct types of mono-alkylated amides, viz.:



These differ as regards physical and chemical properties; they are isomeric. Compounds of type I closely resemble the original amides; compounds of type II are usually known as **imino ethers**, and differ to a large extent (this Chap., G.).

Although esters contain the carbonyl group they do not form oximes with hydroxylamine, but yield hydroxamic acids:



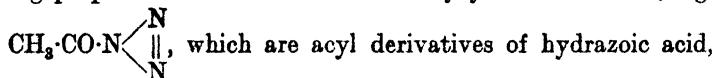
**Formamide** (*Methane-amide*),  $\text{HCO}\cdot\text{NH}_2$ , is a liquid readily soluble in water and alcohol. It boils with partial decomposition at about  $200^\circ$ . When quickly heated it decomposes into CO and  $\text{NH}_3$ , and with phosphorus pentoxide it yields hydrocyanic acid.

**Acetamide**, *Ethane-amide*,  $\text{CH}_3\cdot\text{CO}\cdot\text{NH}_2$ , forms long needles, readily soluble in water and alcohol. It melts at  $82^\circ$ , boils at  $222^\circ$ , and when pure has no odour.

**Di-acetamide**,  $(\text{C}_2\text{H}_3\text{O})_2\text{NH}$ . M.-pt.  $78^\circ$ ; b.-pt.  $223^\circ$ .

## HYDRAZIDES

Just as ammonia by the introduction of acyl groups yields the acid amides, so hydrazine yields the acyl **hydrazides**, e.g. acetyl hydrazine or **acet-hydrazide**,  $\text{CH}_3\cdot\text{CO}\cdot\text{NH}\cdot\text{NH}_2$ . They are formed by the action of esters on hydrazine. They are basic in character, are readily hydrolysed, and possess reducing properties. With nitrous acid they yield **acid azides**, e.g.



( $\text{N}_3\text{H}$ ). (Cf. Curtius, J. pr., 1916, **94**, 273; 1917, **95**, 168, 327.)

All 4 hydrogen atoms in hydrazine can be replaced by acyl radicals in much the same manner as the 3 hydrogen atoms in the ammonia molecule can, e.g. **tetra-acet-hydrazide**,  $\text{Ac}_2\text{N}\cdot\text{N}\cdot\text{Ac}_2$ .



## F. Amido-chlorides and Imido-chlorides

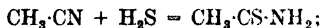
By the action of  $\text{PCl}_5$  upon the primary amides an exchange of  $\text{Cl}_2$  for O takes place, giving rise in the first instance to the so-called **amido-chlorides**, e.g. **acetdichloroamide**,  $\text{CH}_3\cdot\text{CCl}_2\cdot\text{NH}_2$ ; these are extremely unstable compounds, being converted by water into amide and hydrochloric acid, and readily giving up  $\text{HCl}$ , with formation of **imido-chlorides**, e.g.  $\text{CH}_3\cdot\text{CCl}:\text{NH}$ , **acetchloroimide**. The imido-chlorides are also relatively unstable, yielding with water the amide and hydrochloric acid. When heated, they break up into nitrile and hydrochloric acid.

The alkylated amides (p. 210) also yield chloroamides, e.g.  $\text{CH}_3\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_2\text{H}_5$  gives  $\text{CH}_3\cdot\text{CCl}_2\cdot\text{NH}\cdot\text{C}_2\text{H}_5$ , **ethyl acet-chloroamide**, and  $\text{CH}_3\cdot\text{CO}\cdot\text{NR}_2$  gives  $\text{CH}_3\cdot\text{CCl}_2\cdot\text{NR}_2$ ; if these still contain amido-hydrogen, they readily yield imido-chlorides, e.g.  $\text{CH}_3\cdot\text{CCl}:\text{N}\cdot\text{C}_2\text{H}_5$ , **ethyl acetchloroimide**.

The chlorine in these compounds is chemically active; it can be exchanged for sulphur or for an amino group.

## G. Thiamides and Imino-thio-ethers

Thiamides are compounds derived from the amides by the exchange of oxygen for sulphur, e.g.  $\text{CH}_3\cdot\text{CS}\cdot\text{NH}_2$ , **thiacetamide** (*ethane-thion-amide*),  $\text{CH}_3\cdot\text{CS}\cdot\text{NH}\cdot\text{C}_6\text{H}_5$ , **thiacetanilide**. They are mostly crystalline compounds, and are formed by the addition of  $\text{H}_2\text{S}$  to the nitriles (*Cahours*), e.g.:



by treating acid amides with  $\text{P}_2\text{S}_5$ ; from the amido-chlorides, as given above; and by the action of  $\text{H}_2\text{S}$  or  $\text{CS}_2$  upon the amidines. Both simple and alkylated thiamides are known.

When heated alone, they yield a nitrile and sulphuretted hydrogen (compare Elimination of Water from Amides). When hydrolysed with alkalis, they yield the corresponding acid, ammonia (amine) and  $\text{H}_2\text{S}$ , thus:



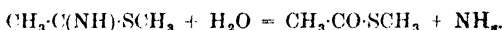
They are rather more acid in character than the amides, and thus many of them are soluble in alkali and yield metallic

derivatives. Consequently, for them, as well as for the amides, the iso-formula  $\text{R} \cdot \text{C} \begin{smallmatrix} \text{SH} \\ \diagup \\ \text{NH} \end{smallmatrix}$  is taken into consideration. From

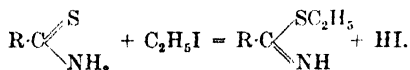
this pseudo form  $\text{R} \cdot \text{C} \begin{smallmatrix} \text{SH} \\ \diagup \\ \text{NH} \end{smallmatrix}$ , **iso-thio acid amides**, are derived

a number of compounds, the **Imino-thio-ethers**, by the replacement of one or both the hydrogen atoms by alkyl groups,

**acetimido-thiomethyl**,  $\text{CH}_3 \cdot \text{C} \begin{smallmatrix} \text{S} \cdot \text{CH}_3 \\ \diagup \\ \text{NH} \end{smallmatrix}$  **methyl iso-thio-acet-anilide**,  $\text{CH}_3 \cdot \text{C} \begin{smallmatrix} \text{S} \cdot \text{CH}_3 \\ \diagup \\ \text{N} \cdot \text{C}_6\text{H}_5 \end{smallmatrix}$  ; They are decomposed by hydrochloric acid into esters of thiacetic acid, thus:



These imino-thio-ethers are prepared by the action of mercaptans upon nitriles in presence of hydrochloric acid gas (*Pinner*), and by the action of alkyl iodides upon thiamides (*Wallach, Bernthsen*):



**Imino-ethers**,  $\text{R} \cdot \text{C} \begin{smallmatrix} \text{NH} \\ \diagup \\ \text{OR}' \end{smallmatrix}$ , which are the oxygen compounds

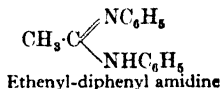
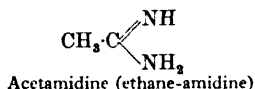
corresponding with the above amino-thio-ethers, and which are isomeric with the alkylated amides, are also known (*Pinner*). They are derived from the pseudo form of the acid amides,

$\text{R} \cdot \text{C} \begin{smallmatrix} \text{NH} \\ \diagup \\ \text{OH} \end{smallmatrix}$ , hypothetical compounds unknown in the free

state, which are isomeric with the simple amides. They are formed by the combination of a nitrile with an alcohol under the influence of hydrochloric acid gas, and in certain cases by alkylating amides; some of them are liquids which boil without decomposition, but others are only known in the form of salts.

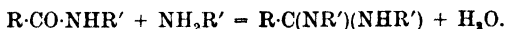
## H. Amidines

Amidines are compounds derived from the amides,  $R \cdot CO \cdot NH_2$ ,  $R \cdot CO \cdot NHR'$ , and  $R \cdot CO \cdot NR'_2$ , by the replacement of oxygen by the bivalent imido-residue  $NH$  or  $(NR)$ :

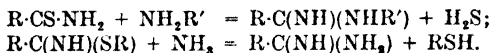


The amidines are well-defined crystalline bases, and form stable salts. Like all acyl derivatives, they are readily hydrolysed, and thus differ from the amines.

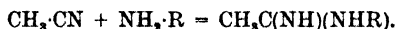
*Formation*.—1. By heating the amides with amines in presence of  $\text{PCl}_3$  (*Hofmann*):



2. By treating the imido-chlorides, thiamides, and iso-thiamides with ammonia or with primary or secondary amines (*Wallach, Bernthsen*), thus:



3. By heating the nitriles with (primary or secondary) amine hydrochloride; this is a particularly easy method when aromatic amines are used, but not in the case of ammonium chloride (*Bernthsen*):



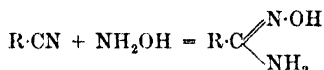
4. By the action of amine bases or ammonia upon iminoethers.

*Behaviour*.—1. They decompose into ammonia or amine and acid when boiled with acids or alkalis (see above), and into ammonia and amide upon boiling with water.

2. The dry compounds, when heated, readily yield ammonia or amine and acid nitrile, so long as the imido-hydrogen atom has not been replaced by alkyl groups.

**Amidoximes** are the compounds formed by the addition of hydroxylamine to nitriles, and, from this mode of formation

and from their properties, appear to be amidines in which an amido- (imido-) hydrogen atom is replaced by hydroxyl:



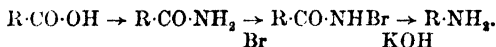
Such an amidoxime is, for instance, isuret,  $\text{NH}_2\cdot\text{CH}:\text{N}\cdot\text{OH}$ , also termed methenyl amidoxime, which is prepared from hydrocyanic acid and hydroxylamine; it is isomeric with carbamide or urea; also ethenyl amidoxime,  $\text{CH}_3\cdot\text{C}(\text{N}\cdot\text{OH})(\text{NH}_2)$ . These compounds are hydrolysed in much the same manner as amidines.

#### CHAIN DEGRADATION AND CHAIN LENGTHENING OF ACIDS

Two processes of interest are chain degradation and chain lengthening of an acid.

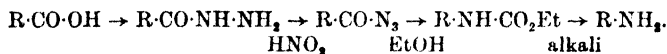
##### 1. Chain degradation.

###### (a) *Hofmann*.

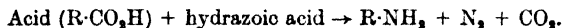


Cf. p. 212.

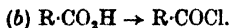
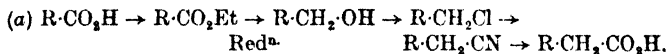
###### (b) *Curtius*.



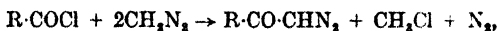
###### (c) *Jensen and Pope*, P. R. S., 1936, 154, A., 54.



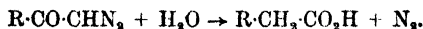
##### 2. Chain Lengthening.



Acid chloride with diazomethane gives acyldiazomethane:



which hydrolyses to acid  $\text{R}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ .



(*Arndt and Eistert*, B., 1935, 200; 1936, 1805.)

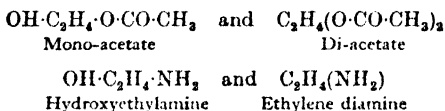
## VIII. POLYHYDRIC ALCOHOLS

A. Dihydric Alcohols or Glycols,  $C_nH_{2n}(OH)_2$ 

The dihydric alcohols may be regarded as derived from the paraffins by the replacement of *two* hydrogen atoms by two hydroxyl groups.

As the monohydric alcohols are often compared with the hydroxides derived from the univalent metals, the glycols may be compared with the hydroxides, derived from the bivalent metals, e.g.  $C_2H_4(OH)_2$  with  $Pb(OH)_2$ . In the saturated dihydric alcohols the hydroxyl groups are attached to a bivalent **alkylene** radical, e.g.  $C_2H_4''$ ,  $C_3H_6''$ , &c.

In many respects they resemble the monohydric alcohols, but they possess these properties in duplicate. Just as, e.g. plumbous hydroxide,  $Pb(OH)_2$ , can give rise to two series of salts, e.g. the basic chloride,  $OH \cdot Pb \cdot Cl$ , and the normal chloride,  $PbCl_2$ , so glycol,  $C_2H_4(OH)_2$ , can give rise to two chlorides,  $OH \cdot C_2H_4 \cdot Cl$  and  $C_2H_4Cl_2$ , known respectively as glycol monochlorhydrin and glycol dichlorhydrin or ethylene dichloride. Similarly, with the acetates and amines derived from glycol:



and similarly with other glycols.

The glycols, as alcohols, give rise to each type of alcoholic derivative; but when, for example, the formation of an ester such as glycollic monoacetate has taken place, this still behaves as a monohydric alcohol, yielding, e.g. with a second molecule of acid, a new ester; it is therefore termed an **ester-alcohol**.

It is not necessary that both the groups which replace the hydrogen or hydroxyl should be of the same nature; thus a mixed derivative of the composition  $NH_2 \cdot C_2H_4 \cdot SO_2 \cdot OH$ , possesses at one and the same time the character of an amine and of a sulphonic acid.

The glycols are mostly thick liquids of sweetish taste, a few only being solid crystalline compounds; they dissolve readily

in water and alcohol, but are only sparingly soluble in ether. It will be found that the solubility of a compound in water tends to increase, and its solubility in ether to decrease, with the number of hydroxyl groups present in the molecule of the compound. Their boiling-points are much higher than those of the corresponding monohydric alcohols, just as these latter possess considerably higher boiling-points than the hydrocarbons from which they are derived.

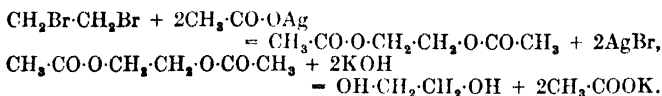
*Constitution.*—As already stated, the glycols contain two hydroxyl groups in each molecule; the arguments in favour of the presence of these hydroxyl groups are exactly similar to those used in the study of the constitution of ethyl alcohol, and are based mainly on certain methods of formation, and on the chief chemical characteristics of the compounds.

Glycols which contain two hydroxyls linked to the same carbon atom are, as a rule, incapable of existence, and are only known in derivatives (see p. 146). Instead of the glycols  $\text{CH}_2(\text{OH})_2$  and  $\text{CH}_3\cdot\text{CH}(\text{OH})_2$ , (the aldehyde hydrates) the aldehydes,  $\text{CH}_2:\text{O}$  and  $\text{CH}_3\cdot\text{CH}:\text{O}$  are formed. An exception is chloral hydrate,  $\text{CCl}_3\cdot\text{CH}(\text{OH})_2$ , which is relatively stable (p. 153). All glycols contain their hydroxyls attached to two different carbon atoms. Glycol itself has thus the constitution  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , which can be proved directly by transforming it, by means of hydrochloric acid, into glycol chlorhydrin,  $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{OH}$ , and oxidizing the latter to monochloroacetic acid,  $\text{CH}_2\text{Cl}\cdot\text{CO}\cdot\text{OH}$ . In this last compound the chlorine and hydroxyl are united to different carbon atoms, and consequently the same applies to glycol chlorhydrin and to the two hydroxyl groups of glycol.

The monohydric alcohols are distinguished as primary, secondary, and tertiary. The glycols may in the same way be characterized as **di-primary** when they contain the group  $\text{CH}_2\cdot\text{OH}$  twice, as in glycol; as **primary-secondary** when they contain the group  $\text{CH}_2\cdot\text{OH}$  together with the group  $\text{CH}\cdot\text{OH}$ , as in propylene glycol,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\text{OH}$ ; further as **di-secondary**, **primary-tertiary**, **secondary-tertiary**, and **di-tertiary**. The structure of a glycol is usually determined by an examination of its oxidation products (pp. 221 and 236).

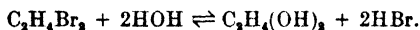
*Modes of Formation.*—1. From the di-halogen-substituted derivatives of the paraffins, in which the two halogen atoms are attached to two different carbon atoms, e.g. ethylene bromide:

(a) By transformation into the di-acetates by means of silver or potassium acetate, and hydrolysis of the ester so produced by potash, baryta, or alcoholic sodium ethoxide (*Bainbridge*, J. C. S., 1914, 2291; *Mereschkowsky*, A., 1923, 431, 231.



A convenient method is to boil the diacetate with ethyl alcohol and a little mineral acid when alcoholysis occurs and ethyl acetate and the glycol are formed (cf. p. 203).

(b) By boiling with water and lead oxide or potassium carbonate. These reagents serve to neutralize the acid as it is formed, and so the reaction is facilitated:



2. In the reduction of ketones to secondary alcohols, the so-called pinacones, i.e. di-tertiary glycols, are obtained as by-products (see pp. 79 and 158), thus:

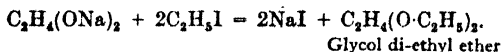


3. By the careful oxidation of olefines by means of very dilute  $\text{KMnO}_4$  (p. 48, or by perhydrol, J. C. S., 1926, 1833; 1930, 2545):



*Behaviour.*—1. As in the case of the monohydric alcohols, the hydrogen of the hydroxylic groups is directly replaceable by potassium or sodium, with the formation of **alcoholates**, e.g.  $\text{OH}\cdot\text{C}_2\text{H}_4\cdot\text{ONa}$  and  $\text{C}_2\text{H}_4(\text{ONa})_2$ , **sodium** and **di-sodium glycols**.

2. The metal in these compounds may be exchanged for new alkyl groups by treatment with alkyl iodide, when glycollic ethers are obtained:



These ethers, like those of the monohydric alcohols, are stable, and cannot be hydrolysed by dilute mineral acids or alkalis.

3. Acids act upon them to produce esters, which are either normal esters or ester-alcohols (see p. 218).

The halogen esters of the glycols are termed chlor-, brom-, or iodhydrins, e.g. glycol chlorhydrin,  $C_2H_4Cl(OH)$ , glycol dichlorhydrin,  $C_2H_4Cl_2$ , &c. The ester-alcohols which are formed by the action of halogen hydride may also be regarded as mono-substitution products of the monohydric alcohols, which cannot be prepared by direct chlorination, e.g.  $C_2H_4Cl(OH)$ , monochlorethyl alcohol. Similarly the di-halogen esters,  $CH_2Cl \cdot CH_2Cl$ ,  $CH_2Br \cdot CH_2Br$ , &c., are the di-substitution products of the paraffins, viz. ethylene dichloride and dibromide.

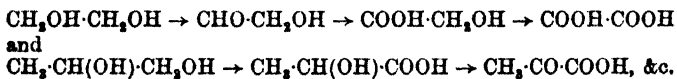
4. As the halogen atoms in the chlor-, brom-, and iodhydrins are readily replaceable, just as in  $C_2H_5Cl$  or  $C_2H_5I$ , these compounds may be used for the preparation of most of the other glycol derivatives; thus they yield thio-glycols with potassium hydrosulphide, amines with ammonia, sulphonic acids with sodium bisulphite, and nitriles with potassium cyanide.

5. Alkalis react with the glycol monochlorhydrins, and by the elimination of  $HCl$  yield cyclic anhydrides, e.g. **ethylene**

**oxide**,  $\begin{array}{c} CH_2 \\ | \\ CH_2 \end{array} \rangle O$ . It is interesting to note that these anhydrides

cannot be obtained by the elimination of water from the glycols themselves. When ethylene glycol is heated with zinc chloride at  $230^\circ$  water is eliminated, and the product obtained is acet-aldehyde (or a polymer). This reaction is explained by assuming the intermediate formation of unsaturated alcohols which are not in themselves capable of existence, e.g.  $CH_2:CH(OH)$ , but which immediately undergo transformation into the isomeric aldehydes or ketones:  $CH_2:CH \cdot OH = CH_3 \cdot CH:O$ .

6. As alcohols the glycols are readily oxidized. If they contain the primary alcoholic group, they can yield aldehydes and acids containing the same number of carbon atoms. If they contain a secondary alcoholic group, they yield ketones, e.g.:




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**Methylene- and Ethylidene-glycol.** (See Aldehydes, Chap. V, A.)



**Ethylene glycol** (*glycol*),  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$  (*Wurtz*), A., 100, 110), b.-pt.  $197.5^\circ$ , is prepared from ethylene bromide by method 1a (p. 220). For properties, see above. Its formula has been corroborated by the determination of its vapour density. Oxidizing agents transform it into glycollic acid,  $\text{OH}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OH}$ , and oxalic acid,  $\text{OH}\cdot\text{CO}\cdot\text{CO}\cdot\text{OH}$ .

Glycol is manufactured on the large scale from ethylene and chlorine water; the chlorhydrin  $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{OH}$  so formed yields glycol when boiled with milk of lime. It is largely used for preventing ice formation, e.g. on aeroplane edges, and also as a dielectric in electrolytic condensers, and for the production of various ethers and esters used in the cellulose industry, e.g. mono and diethyl ethers, mono-tertiary butyl ether,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}\cdot\text{C}(\text{CH}_3)_3$ , formed by the union of glycol with tertiary butylene,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{C}(\text{CH}_3)_2\cdot\text{C}(\text{CH}_3)_2$ . Also the monoacetate and the acetate of the monomethyl ether.

**Propylene glycol** is known in two isomeric forms, viz.

(a) **Trimethylene glycol**,  $\beta$ -**Propylene glycol**, *Propane-1:3-diol*,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , which is prepared from trimethylene bromide, and is a di-primary glycol boiling at  $216^\circ$ . It is also produced by the *Schizomycetes* fermentation of glycerol (M., 1881, 636; B., 1912, 3115).

(b)  $\alpha$ -**Propylene glycol** *Propane-1:2-diol*,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{OH}$ , can be prepared from propylene bromide, but is more easily obtained by distilling glycerol with caustic soda or from propylene and aqueous chlorine. It boils at  $188^\circ$ . It contains an asymmetric carbon atom in the molecule, and becomes optically (-) active when fermented, i.e. certain bacteria destroy the dextro modification more rapidly than the laevo.

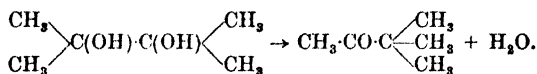
Four **butylene glycols**, and various **amylen-** and **hexylene-glycols**, &c., are also known. Of these, the  $\gamma$ -glycols (in which the hydroxyls are in the positions 1:4, and which therefore contain the grouping  $\underset{1}{\text{C}}(\text{OH})\cdot\underset{2}{\text{C}}\cdot\underset{3}{\text{C}}\cdot\underset{4}{\text{C}}(\text{OH})$ ) yield compounds

of the **furane** series by the formation of anhydrides (B., 1889, 2567), and therefore stand in close relation to thiophene and pyrrole, Chap. XL.

1:3-butylene glycol obtained by the hydrogenation of alcohol (Chap. XLIX, A.) is used in the form of its diacetate as a high boiling solvent for acetyl- and nitro-cellulose.

**Pinacone**, **Tetramethyl-ethylene glycol** (2:3-*Dimethyl-*

*butane-2:3-diol*,  $(\text{CH}_3)_2\text{C}(\text{OH})\cdot\text{C}(\text{OH}):(\text{CH}_3)_2$ . The hydrate,  $(+ 6\text{H}_2\text{O})$ , forms large quadratic tables; in the anhydrous state it is a crystalline mass melting at  $38^\circ$  and boiling at  $172^\circ$ . When warmed with dilute sulphuric or hydrochloric acid it yields pinacolone,  $\text{CH}_3\cdot\text{CO}\cdot\text{C}(\text{CH}_3)_3$ , methyl tertiary-butyl ketone or 2:2-dimethyl-butan-3-one (see p. 162, and Chap. XXXVIII):



In this reaction an interesting intramolecular rearrangement occurs, together with the elimination of water.

Numerous other pinacones are known. They may be obtained by reducing ketones or synthetically (*Lieben*, M. 17, 68; 19, 16), and with acids yield the corresponding pinacolines.

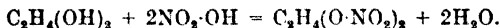
#### DERIVATIVES OF THE GLYCOLS

The **ethers**, e.g.  $\text{C}_2\text{H}_4(\text{OCH}_3)_2$ , are mostly colourless liquids with ethereal odours, and have lower boiling-points than the glycols. (Cf. Ether and Ethyl Alcohol.) They cannot be readily hydrolysed. The **esters**, e.g.  $\text{C}_2\text{H}_3(\text{O}\cdot\text{CO}\cdot\text{CH}_3)_2$ , are also mostly liquids, and are readily hydrolysed.

The following esters of inorganic acids are interesting:

**Glycol chlorhydrin**,  $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{OH}$ , obtained by passing hydrogen chloride into warm glycol, or on the large scale by the addition of hypochlorous acid to ethylene, is a liquid miscible with water, and boiling at  $130^\circ$ ; in this last respect differing from its corresponding alcohol to almost the same extent as ethyl chloride does from alcohol.

**Glycollic di-nitrate**,  $\text{C}_2\text{H}_4(\text{NO}_3)_2$ , is prepared by acting on glycol with sulphuric and nitric acids:



It is a yellowish liquid, insoluble in water, is readily hydrolysed by alkalis to glycol and nitric acid, and hence the constitution. The formation of such nitric esters, which are highly explosive, is characteristic of the polyhydric alcohols (see Nitroglycerine, p. 231).

**Ethylene cyanide**,  $\text{CN}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}$ , obtained by the action of potassium cyanide on ethylene dibromide is a

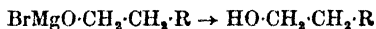
crystalline solid, and on hydrolysis with alkalis yields  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , succinic acid, and hence may be regarded as **succinonitrile**.

Other esters are used in industry, e.g. the succinate,  $\text{CH}_2\cdot\text{CO}\cdot\text{O}\cdot\text{CH}_2$   
 $\begin{array}{c} | \qquad \qquad | \\ \text{CH}_2\cdot\text{CO}\cdot\text{O}\cdot\text{CH}_2 \end{array}$ , and similar compounds used in the plastics industry (Glyptalresins, Chap. LX, C4), and the oleate and succinate used for emulsifying oils and as detergents.

**Ethylene oxide**,  $\text{C}_2\text{H}_4\text{O}$ , the inner anhydride of ethylene glycol,  $\begin{array}{c} \text{H}_2\text{C} \\ | \qquad \diagup \\ \text{H}_2\text{C} \end{array} \text{O}$ , is obtained by distilling glycolchlorhydrin

with potassium hydroxide solution or by passing ethylene, steam and air over silver oxide at  $200^\circ$  and 600–700 lb. pressure. It has an ethereal odour, boils at  $10.7^\circ$ , is miscible with water, but gradually forms glycol.

In many respects ethylene oxide reacts as an unsaturated compound and readily forms additive products with hydrogen, water, halogen hydriacids, alcohols, ammonia, amines, Grignard reagents, &c. The reaction involves an opening of the ring and as a rule the union of hydrogen with the O and the other radical with the carbon resulting in the formation of derivatives of glycol; thus with water glycol itself is formed, with hydrogen chloride glycol chlorhydrin, with alcohol glycol monoethyl ether  $\text{HO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OEt}$ , with acetic acid monoacetyl-glycol  $\text{HO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OAc}$ , and with hydrogen cyanide  $\beta$ -hydroxy-propionitrile  $\text{HO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}$ , isomeric with the nitrile of ordinary lactic acid (Chap. IX, A.). The oxide is thus an important synthetical reagent for preparing glycol derivatives. The additive compounds with *Grignard* reagents are of importance as on treatment with water they yield higher alcohols



when R can be any alkyl group from  $\text{CH}_3$  to  $\text{C}_5\text{H}_{11}$ .

The structure of these different additive compounds, viz. ethylene additive compounds, is a strong argument in favour of the cyclic structure of the oxide and not the open-chain structure  $\text{CH}_2\text{:CH}\cdot\text{OH}$  which is given to vinyl alcohol (Chap. III, B.).

Some of the higher homologues of ethylene oxide with larger

rings are more stable as in the case of polymethylene compounds (Chaps. XVI and XXXIII).

Cyclic ethers are often formed by the action of peroxides, e.g. perbenzoic acid,  $C_6H_5 \cdot CO \cdot O \cdot OH$ , on olefines.

An ether of some importance is *p*-dioxane  $O \begin{array}{c} \diagup CH_2 \cdot CH_2 \\ \diagdown CH_2 \cdot CH_2 \end{array} O$ ,

b.-pt.  $101.5^\circ$ . It is used as a solvent for cellulose acetate, but is liable to explosions, and can be prepared from glycol chlorhydrin, with sulphuric acid; this yields  $\beta\beta'$ -dichloroethyl ether  $ClCH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2Cl$ , which with 5 per cent sodium hydroxide solution yields the cyclic ether. Similarly  $\beta\beta'$ -di-

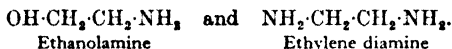
chloropropyl ether yields dimethyldioxane,  $O \begin{array}{c} \diagup CH_2 \cdot CHMe \\ \diagdown CH_2 \cdot CHMe \end{array} O$

and chloromethyl- $\beta$ -chloroethyl ether yields  $O \begin{array}{c} \diagup CH_2 \cdot CH_2 \\ \diagdown CH_2 \cdot CH_2 \end{array} O$ , methylene ethylene dioxide.

The hydrate of dioxane,  $OH \cdot CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$ , **diethyleneglycol**, b.-pt.  $244.5^\circ$ , is formed by the union of ethylene oxide and ethylene glycol, and the monoethyl and monobutyl ethers are commercial products known as *Carbitol* and *butylcarbitol*. On catalytic dehydration the glycol yields dioxane.

## AMINES OF THE DIHYDRIC ALCOHOLS

These are derived from glycols by the replacement of one or both hydroxyl groups by amino groups:



In the former case compounds are obtained which possess the properties of an amine in addition to those of an alcohol; in the latter, diamines free from oxygen, which are analogous to ethylamine, but are di-acid and not mono-acid bases.

The ethanolamines are formed by the action of aqueous ammonia on ethylene oxide. Ethanolamine,  $OH \cdot CH_2 \cdot CH_2 \cdot NH_2$ , b.-pt.  $171^\circ$ ; diethanolamine,  $(OH \cdot CH_2 \cdot CH_2)_2NH$ , b.-pt.  $268^\circ$ , and triethanolamine,  $(OH \cdot CH_2 \cdot CH_2)_3N$ , b.-pt.  $208/16$  mm. The last is used commercially in the form of its salts with palmitic, stearic and oleic acids as these neutral soaps are good emulsifiers and detergents.



$\gamma$ -glycol, it is closely related to pyrrole, from which it is formed by the action of hydroxylamine (whereby a dioxime is first produced), and subsequent reduction (B., 1889, 1968).

**Pentamethylene diamine**, *cadaverine*,  $\text{NH}_2 \cdot (\text{CH}_2)_5 \cdot \text{NH}_2$ , is formed by the reduction of trimethylene cyanide,  $\text{CN} \cdot (\text{CH}_2)_3 \cdot \text{CN}$ , which on its part is prepared from trimethylene bromide,  $\text{CH}_2\text{Br} \cdot \text{CH}_2 \cdot \text{CH}_2\text{Br}$ , and KCN (*Ladenburg*). It is a colourless syrupy liquid of very pronounced spermaceti and piperidine odour, solidifies in the cold, and boils at  $178^\circ$ – $179^\circ$ . It possesses especial interest, because, being a  $\delta$ -diamine, it gives up ammonia

and yields the cyclic base **piperidine**,  $\text{CH}_2 \begin{array}{c} \diagup \text{CH}_2 \cdot \text{CH}_2 \\ \diagdown \text{CH}_2 \cdot \text{CH}_2 \end{array} \text{NH}$  (see Chap. XLIII, B.).

Many of these polyacid bases are found in decaying albumen and in corpses, and are designated **ptomaines** or **toxines**.

**Choline**, *bilincurine*, *ethylol-trimethyl-ammonium hydroxide*,  $\text{OH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NMe}_3 \cdot \text{OH}$  (*Strecker*), is found in the bile ( $\chi\omicron\lambda\eta$ , bile,) brain, yolk of egg, &c., being present in these combined with fatty acids and glyceryl-phosphoric acid as lecithin. It is also found in herring brine, hops, beer, and in many fungi, &c., and is obtained by boiling sinapine with alkalis (the old name for this product was "Sincaline"). Choline is a strong, deliquescent base, and readily absorbs carbon dioxide from the air. It is not poisonous. Its acetyl derivative is an important hormone of the animal tissues (Chap. LXVIII, B.).

**Neurine** ( $\nu\epsilon\iota\upsilon\rho\omicron\nu$ , nerve), *trimethyl-vinyl-ammonium hydroxide*,  $\text{CH}_2 \cdot \text{CH} \cdot \text{NMe}_3 \cdot \text{OH}$  (*Hofmann*), containing the unsaturated vinyl radical, is very similar to choline, and can be prepared from brain substance or from choline by the action of HI followed by moist silver oxide; it is only known in solution, and is very poisonous. It can be re-transformed into choline.

**Taurine**,  $\text{HO} \cdot \text{SO}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NH}_2$  (*Gmelin*), is present in combination with cholic acid (Chap. LXII, B.) as **taurocholic acid** in the bile of oxen and many other animals, also in the kidneys, lungs, &c. It crystallizes in large monoclinic prisms, and is readily soluble in hot water. Its constitution follows from its synthesis from  $\beta$ -bromo-ethylamine and ammonium sulphite or from ammonia and  $\beta$ -bromo-ethyl-sulphonic acid, viz.  **$\beta$ -amino-ethylsulphonic acid**. It is a typical amphoteric substance, i.e. both base and acid, and is probably an inner salt formed by the neutralization by the  $\text{NH}_2$  group of the acid:

**Isethionic acid**, hydroxy-ethyl-sulphonic acid,  $\text{OH} \cdot \text{CH}_2 \cdot$

$\text{CH}_2\cdot\text{SO}_2\cdot\text{OH}$ , obtained when carbyl sulphate,  $\text{C}_2\text{H}_4\text{S}_2\text{O}_6$  (from  $\text{C}_2\text{H}_4$  and  $\text{SO}_3$ ), is boiled with water; its constitution follows from its properties, and also from the fact that it may be obtained by the oxidation of the hydroxymercaptan,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{SH}$ . By the action of  $\text{PCl}_5$  followed by ammonia it yields taurine:



Numerous unsaturated glycols of the type,  $\text{OH}\cdot\text{CHMe}\cdot\text{C}:\text{C}\cdot\text{CHMe}\cdot\text{OH}$ , have been prepared by the action of aldehydes or ketones on the *Grignard* compounds,  $\text{Br}\cdot\text{MgC}:\text{C}\cdot\text{MgBr}$ , derived from acetylene (*Iocitsch*, *Annales*, 1913, VIII, 30).

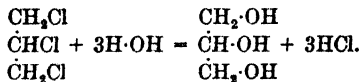
## B. Trihydric Alcohols

The molecule of each trihydric alcohol contains three hydroxyl groups, each attached to a different carbon atom. They may be regarded as analogous to the hydroxides of trivalent metals, e.g.  $\text{C}_3\text{H}_5(\text{OH})_3$  and  $\text{Al}(\text{OH})_3$ . They can give rise to three distinct groups of derivatives according as one, two, or three of the hydroxyls react, e.g. chlorides— $\text{C}_3\text{H}_5\text{Cl}(\text{OH})_2$ , monochlorhydrin;  $\text{C}_3\text{H}_5\text{Cl}_2\cdot\text{OH}$ , dichlorhydrin; and  $\text{C}_3\text{H}_5\text{Cl}_3$ , trichlorhydrin of glycerol. Similarly for acetates, amino-derivatives, &c.

Although the compound  $\text{CH}(\text{OH})_3$ , **ortho-formic acid**, is not known, derivatives, e.g. **ethyl ortho-formate**,  $\text{CH}(\text{OEt})_3$ , (p. 166), and similarly **ethyl ortho-acetate**,  $\text{CH}_3\cdot\text{C}(\text{OEt})_3$ , can readily be prepared.

**Glycerine**, *glycerol*, *propane-1 : 2 : 3-triol*  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{OH}$ . (*Scheele*, 1779; formula established by *Pelouze* in 1836, and constitution by *Berthelot* and *Wurtz*.)

*Synthesis*.—By heating 1 : 2 : 3-trichloropropane with water to  $170^\circ$ :

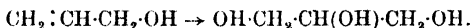


The trichloropropane is itself obtainable from isopropyl iodide (which can also be prepared synthetically) by conversion into propylene, addition of  $\text{Cl}_2$ , and heating the propylene dichloride

thus formed with iodine chloride (*Friedel and Silva*, Bull. Soc. Chim., **20**, 98):



Glycerol is also produced when allyl alcohol is oxidized with very dilute potassium permanganate:



The *constitution* of glycerol follows from these syntheses and also from its relation to tartronic acid (p. 230): each of the three hydroxyls is attached to a separate carbon atom.

*Manufacture*.—It is a by-product in the manufacture of hard soaps (p. 184), and crude glycerine is made by concentrating the waste lyes in suitable salting-out evaporators, from which the common salt can be removed as it is formed. It is also a by-product in the manufacture of stearic acid for candles. The oils or fats are hydrolysed by one of the methods mentioned on p. 184, particularly by the Twitchell process. The crude, neutral glycerine liquor, after removal of the fatty acids, is concentrated under reduced pressure as glycerine vaporizes at 100°, and the crude, concentrated product is refined by distillation with superheated steam under reduced pressure; the distillate is again concentrated, and, if necessary, filtered through animal charcoal.

A biochemical method is by the alcoholic fermentation of glucose. In the ordinary fermentation, by means of yeast (p. 84), a 3 per cent yield of glycerol is obtained, but this is easily increased to 24 per cent by the addition of small amounts of sodium sulphite (*Helv.*, 1919, 167) or of sodium carbonate at intervals (*J. S. C. I.*, 1919, 175R.)

*Properties*.—It is a thick, colourless syrup, of specific gravity 1.26, solidifies, when strongly cooled, to crystals, like those of sugar-candy, which melt at 17.9°. It boils at 290°, but is best distilled under diminished pressure, e.g. at 170°/12 mm. It is very hygroscopic, and mixes with water and alcohol in all proportions, but is insoluble in ether.

*Uses*.—In the manufacture of liqueurs, fruit preserves, wine, cakes; for non-drying stamp colours and blacking; when mixed with glue, in book printing; as a healing ointment for external use in pharmacy, for cosmetics; but especially in the manufacture of nitro-glycerine and in the colour industry, and as an antifreeze. (*J. S. C. I.*, 1928, 1073.)



It is used in the preparation of allyl alcohol (p. 91), acrolein (p. 154), allyl iodide (p. 70), isopropyl iodide (p. 65), and formic acid (p. 173) (C. I., 1930, 1021, 1069; 1931, 949).

*Behaviour.*—1. With alkalis and other metallic hydroxides it forms **alcoholates**, which are readily decomposed again into their components.

2. As a trihydric alcohol the hydrogen atoms of the OH groups can be replaced by alkyl radicals yielding **ethers**, e.g. **mono-ethylin**,  $C_3H_5(OH)_2(OC_2H_5)$ , and **triethylin**,  $C_3H_5(OC_2H_5)_3$ , liquids which boil without decomposition.

3. As an alcohol it forms a great variety of **esters**: thus, with sulphuric acid, the easily saponifiable **glyceryl-sulphuric acid**,  $C_3H_5(OH)_2(O\cdot SO_3H)$ ; with phosphoric acid, **glyceryl-phosphoric acid**,  $C_3H_5(OH)_2(O\cdot PO_3H_2)$ ; with nitric acid, **glyceryl trinitrate**,  $C_3H_5(O\cdot NO_2)_3$ ; with hydrochloric acid the **chlorhydrins**; and with the higher fatty acids the fats. For its behaviour with hydriodic acid, or iodine and phosphorus, see p. 65.

4. It yields compounds of a mercaptan or aminic character by exchange of OH for SH or  $NH_2$ .

5. When distilled with dehydrating agents, e.g. phosphorus pentoxide, or, better, anhydrous potassium hydrogen sulphate, two molecules of water are eliminated from each molecule of glycerol, and acrolein (p. 153) is formed. By the indirect separation of one mol.  $H_2O$ , **glycide alcohol**,  $C_3H_6O_2$ , is obtained.

6. Oxidizing agents convert it, according to conditions, either into **glyceric**,  $OH\cdot CH_2\cdot CH(OH)\cdot CO_2H$ , **tartronic**,  $CO_2H\cdot CH(OH)\cdot CO_2H$ , or **mesoxalic acid**,  $CO_2H\cdot CO\cdot CO_2H$ , or acids with a smaller number of carbon atoms. The formation of the three above-mentioned acids indicates that the glycerol molecule must be built up of two primary and one secondary alcoholic groups, as represented in the formula already given. Halogens oxidize and do not substitute.

## DERIVATIVES

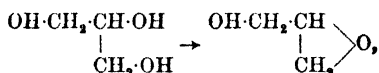
**Chlorhydrins** (hydrochloric esters). **Mono-** and **dichlorhydrins** are formed by the action of hydrochloric acid on glycerol, and **trichlorhydrin** by the action of phosphorus pentachloride on the mono- or di-compounds. Each of the two first-named exists in two isomeric modifications.

**$\alpha$ -Monochlorhydrin**, **3-Chloro-propane-1:2-diol**,  $CH_2(OH)\cdot$

$\text{CH(OH)·CH}_2\text{Cl}$ , is formed from epichlorhydrin,  $\text{C}_3\text{H}_5\text{O·Cl}$  (see below), and water;  $\alpha$ -**dichlorhydrin**, 1:3-dichloro-propane-2-ol,  $\text{CH}_2\text{Cl·CH(OH)·CH}_2\text{Cl}$ , from epichlorhydrin and  $\text{HCl}$ ;  $\beta$ -**monochlorhydrin**,  $\text{CH}_2(\text{OH})\text{·CHCl·CH}_2(\text{OH})$ , and  $\beta$ -**dichlorhydrin**,  $\text{CH}_2\text{Cl·CHCl·CH}_2\text{·OH}$ , by the addition of hypochlorous acid to allyl alcohol or to allyl chloride.

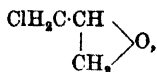
The chlorhydrins are liquids sparingly soluble in water, and readily soluble in alcohol and ether. Their boiling-points are much below that of glycerol.

**Glycidic Compounds.**—By the elimination of water from glycerol a compound is obtained which unites within itself the properties of ethylene oxide and of a monohydric alcohol, viz. **glycidic alcohol**. It is a 1:2-cyclic oxide or ether,



and is isomeric with propionic acid.

It may be prepared by the abstraction of  $\text{HCl}$  from  $\alpha$ -monochlorhydrin by means of baryta, just as ethylene chlorhydrin yields ethylene oxide. It is a colourless liquid, boiling at  $162^\circ$ , and miscible with water, alcohol, and ether. It combines with  $\text{H}_2\text{O}$ , yielding glycerol, and with  $\text{HCl}$  yielding the chlorhydrin, and, as an alcohol, forms esters (glucide esters), &c. Its hydrochloric ester is **epichlorhydrin**,



isomeric with chloroacetone and propionyl chloride, a mobile liquid of chloroform odour, boiling at  $117^\circ$ , which is formed by the elimination of  $\text{HCl}$  from either of the dichlorhydrins. Like ethylene oxide it is capable of combining with  $\text{H}_2\text{O}$ ,  $\text{HCl}$ , &c.

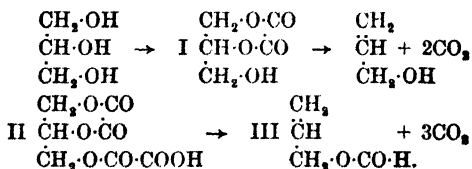
**Esters of Nitric Acid.**—**Mononitrin**,  $\text{C}_3\text{H}_5(\text{OH})_2(\text{O·NO}_2)$ , and **trinitrin** or glyceryl trinitrate usually termed **nitroglycerine**,  $\text{C}_3\text{H}_5(\text{O·NO}_2)_3$ , are known. The latter is prepared by treating glycerol with a cold mixture of concentrated nitric and sulphuric acids. It is a colourless oil, insoluble in water, poisonous, and of a sweet, burning, aromatic taste. Sp. gr. 1.6. M.-pt. about  $13.2^\circ$ . It solidifies on cooling, and exists in two physical crystalline isomerides (*Hepworth*, J. C. S., 1919, 840). It burns without explosion, but explodes with terrible violence when quickly heated or when struck (*Nobel's* explosive

oil). When mixed with kieselguhr in the proportion of three parts to one it forms **dynamite** (Nobel, 1867), which is exploded by fulminate of mercury with frightful force. Modern dynamite consists of glyceryl nitrate absorbed in wood pulp, and often contains small amounts of glycol dinitrate (Chap. VIII, A.) to prevent the solidifying of the nitroglycerine in cold weather, and inorganic nitrates. Blasting gelatine contains about 8 per cent of nitro-cellulose (Chap. XIV) in addition to nitroglycerine. The nitrate is hydrolysed by alkalis and by ammonium sulphide, yielding glycerol and nitric acid, and hence its constitution as a nitrate,  $C_3H_5(O\cdot NO_2)_3$ , and not a nitro-derivative, e.g.  $C_3H_2(NO_2)_3(OH)_3$ .

The natural glycerides are mostly normal esters, e.g. **glyceryl tripalmitate**, **tripalmitin**,  $C_3H_5(O\cdot CO\cdot C_{15}H_{31})_3$ , **tristearin**, &c. (see p. 183 *et seq.*). These esters can also be obtained artificially, as can also the mono- and dihydric esters, e.g. **monopalmitin**,  $(OH)_2C_3H_5\cdot O\cdot CO\cdot C_{15}H_{31}$ , and **dipalmitin**,  $OH\cdot C_3H_5(O\cdot CO\cdot C_{15}H_{31})_2$ , and mixed glycerides (Chap. LV, C.).

Most are wax-like solids, and, on hydrolysis, yield as ultimate products glycerol and the fatty acids. With the normal esters this hydrolysis occurs in stages yielding the mono-hydroxy ester, then the dihydroxy, and finally glycerol.

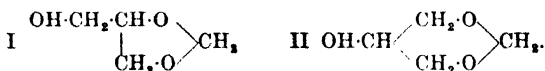
Glyceryl oxalates play an important part in the conversion of oxalic acid into formic acid and of glycerol into allyl alcohol. The first of these reactions has already been described (p. 173). The formation of allyl alcohol probably proceeds in the following stages. (Chattaway, J. C. S., 1914, 153.) By the action of oxalic acid upon glycerol a certain amount of the neutral oxalate (dioxalin) I is formed in addition to the acid oxalate (pp. 173 and 91). The neutral oxalate decomposes at the higher temperature into carbon dioxide and allyl alcohol. Some of the glycerol may form the trioxalate (trioxalin) II, which then decomposes into carbon dioxide and allyl formate III, which is always formed as a by-product.



The esters of glycerol with succinic acid are used as glyptal or alkyd resins (Plastics, Chap. LX, C4).

The glyceryl esters of phosphoric acid,  $H_3PO_4$ , are compounds of interest as they are related to natural products such as the lecithins (Chap. LV, I.). Both  $\alpha$ - and  $\beta$ -monophosphates, viz.  $OH\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot O\cdot PO(OH)_2$  and  $(OH\cdot CH_2)_2CH\cdot O\cdot PO(OH)_2$ , have been prepared, the former from  $\alpha$ -monochlorhydrin and trisodium phosphate and the latter from phosphoryl chloride, and the  $\alpha$ -dichlorhydrin and subsequent hydrolysis (*King and Pyman, ibid.* 1238; *Bailly, C. R.*, 1915, **161**, 677). For methods of discrimination between  $\alpha$ - and  $\beta$ -glycerophosphates, cf. *Grimbert and Bailly, C. R.*, 1915, **160**, 207.

Glycerol condenses with aldehydes and ketones in the presence of hydrogen chloride, giving both 5 and 6 membered cyclic acetals, e.g. I and II with formalin:



The structure of the compounds was proved by final conversion into  $\beta$ - and  $\alpha$ -methyl ethers of glycerol respectively, after separation by means of their benzoyl derivatives (*J. C. S.*, 1915, 337; *Hibbert and others, J. A. C. S.*, 1928, 2238, 3120, 3376; 1929, 302, 3644; *Fairbourne, J. C. S.*, 1929, 2234). Mono alkyl ethers of glycerol occur in fish oils, e.g. *batyl alcohol* and the unsaturated *selachyl alcohol*, probably as esters with fatty acids.

### C. Tetra-, Penta-, and Haxahydric Alcohols

These alcohols can react respectively with 4, 5, or 6 molecules of a monobasic acid to form neutral esters, and consequently 4, 5, or 6 alcoholic hydroxyls are to be assumed as present in their molecules.

The number of hydroxyls present in an alcohol is usually determined from the number of acetyl groups present in the ester which is formed when the alcohol is heated with acetic anhydride and anhydrous sodium acetate, thus:



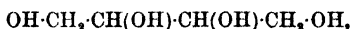
The acetyl derivative is then (a) hydrolysed with alcoholic potash and the amount of potash used up determined by

titration, or (b) distilled with *p*-toluene-sulphonic acid and the acetic acid in the distillate titrated.

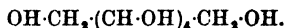
Another method is to prepare the ester of the alcohol in question with the aid of an acid containing halogen, bromobenzoic acid being especially suitable for this; and from the percentage of bromine found in the ester, the number of acyl radicals which have entered the molecule, i.e. the number of hydroxyls, can be deduced.

The polyhydric alcohols are solid crystalline compounds of sweet taste. Many occur as natural products, and they may be obtained by the reduction of the corresponding hydroxy aldehydes, hydroxy ketones, or hydroxy monobasic acids (mannonic acid, &c.) by sodium amalgam. (*E. Fischer*, B., 1889, 2204.) Conversely, cautious oxidation by bromine water transforms them first into sugars (hydroxy-aldehydes), and then into the corresponding acids. As a rule they cannot be volatilized without decomposition. Their derivatives are exactly analogous to those of glycol and glycerol.

Their *constitution* follows from the generalization already repeatedly referred to, viz. that not more than one hydroxyl group can be attached to the same carbon atom without the immediate separation of water, so that a tetrahydric alcohol must contain at least 4, and a hexahydric alcohol at least 6, atoms of carbon. The tetrahydric alcohol erythritol,  $C_4H_6(OH)_4$ , has thus the formula:



and mannitol, the simplest of the hexahydric alcohols,  $C_6H_8(OH)_6$ , the formula



All the common polyhydric alcohols have a normal carbon chain, as on reduction with hydriodic acid they yield normal secondary iodides, e.g. erythritol yields 2-iodo-butane,  $CH_3\cdot CHI\cdot CH_2\cdot CH_3$ .

**1. Tetrahydric Alcohols.**—**Ortho-carbonic ether**,  $C(OC_2H_5)_4$ , is to be regarded as the ether of the hypothetical alcohol,  $C(OH)_4$ , which may be looked upon as the hydrate of carbonic acid, but is itself incapable of existence. It is a liquid of ethereal odour, boiling at  $159^\circ$ .

**Erythritol** (*Butane-tetrol*) occurs in the free state in *Proto-coccus vulgaris*, and combined with orsellinic acid as an ester

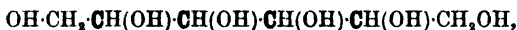
(erythrin), in many lichens and algæ. It forms large quadratic crystals, sparingly soluble in alcohol and insoluble in ether. M.-pt.  $112^{\circ}$ ; b.-pt. about  $300^{\circ}$ .

2. **Pentahydric Alcohols**, **Arabitol**,  $\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_3\cdot\text{CH}_2\cdot\text{OH}$  (from arabinose by reduction). **Xylitol**, by the reduction of xylose, is stereo-isomeric; and **rhamnitol**,  $\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_4\cdot\text{CH}_3$ , m.-pt.  $121^{\circ}$ , from rhamnose, is homologous.

3. **Hexahydric Alcohols**. — **Mannitol**,  $\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_4\cdot\text{CH}_2\cdot\text{OH}$  (Proust, 1800), is found in many plants, for instance in the larch, in *Viburnum opulus*, in celery, in the leaves of *Syringa vulgaris*, in sugar-cane, in *Agaricus integer* (of the dry substance of which it forms 20 per cent), in rye bread, and especially in the manna ash, *Fraxinus ornus*, the dried juice of which constitutes manna. It can be prepared from mannose,  $\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_4\cdot\text{CH}\cdot\text{O}$ , by reduction with sodium amalgam.

It crystallizes in fine needles or rhombic prisms, and is readily soluble in cold water and boiling alcohol. It is dextro-rotatory, but a lævo-rotatory and an inactive modification are also known. (See Mannonic Acid.) M.-pt.  $166^{\circ}$ . When heated it is converted into its anhydrides, **mannitan**,  $\text{C}_6\text{H}_{12}\text{O}_5$ , and **mannide**,  $\text{C}_6\text{H}_{10}\text{O}_4$ . Cautious oxidation converts mannitol into a mixture of mannose,  $\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_4\cdot\text{CHO}$ , and fructose,  $\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$ . Nitric acid oxidizes it to saccharic acid,  $\text{CO}_2\text{H}\cdot(\text{CH}\cdot\text{OH})_4\cdot\text{CO}_2\text{H}$ ; hydriodic reduces it to secondary hexyl iodide,  $\text{CH}_3\cdot\text{CHI}\cdot(\text{CH}_2)_3\cdot\text{CH}_3$  (p. 64).

The molecule of mannitol contains 4 asymmetric carbon atoms, e.g.:



and hence a number of stereo-isomerides are known, e.g. *d*-, *l*-, and *r*-mannitol, *d*-, *l*-, *r*-sorbitol and **dulcitol**, which is optically inactive owing to the fact that its molecule is symmetrical in configuration. (Stereochemistry of Sugars, Chap. XIV, A.)

The sugars (monosaccharides) are closely related to the penta- and hexahydric alcohols, being the corresponding polyhydric aldehydes or ketones. The alcohols as a rule are not fermented by yeast, and do not reduce an alkaline cupric solution, dulcitol excepted.

## OXIDATION PRODUCTS OF THE POLYHYDRIC ALCOHOLS

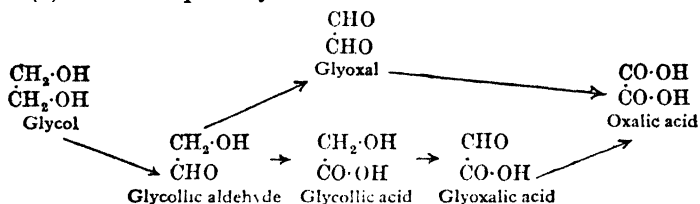
Just as the monohydric alcohols are oxidized to aldehydes, ketones, and acids, so the polyhydric alcohols pass, on oxidation, into aldehydes, ketones, and polybasic acids.

On oxidation the polyhydric alcohols yield not only aldehydes, ketones, and acids, but also compounds with dual functions, i.e. alcohol and acid, alcohol and aldehyde, &c. Examples are the **hydroxy aldehydes**, which are at the same time aldehyde and alcohol, the **hydroxy ketones**, at the same time ketone and alcohol, the **hydroxy acids**, **aldehyde acids**, **ketone acids**, and **ketone aldehydes**.

An aldehyde acid, for instance, is capable, as an acid, of forming salts, esters, and amides on the one hand; and on the other, as an aldehyde, it is able to reduce an ammoniacal silver solution, to combine with  $\text{NaHSO}_3$ , and to react with hydroxylamine, &c.

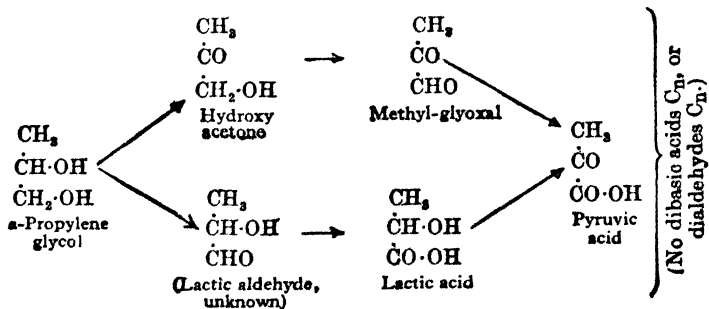
## SUMMARY OF THE OXIDATION PRODUCTS

## (a) Of the di-primary alcohols.



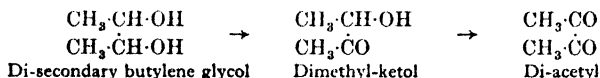
Possible products: Di-aldehydes, dibasic acids, hydroxy aldehydes, hydroxy acids, aldehyde acids.

## (b) Of the primary-secondary alcohols.



Possible products: hydroxy aldehydes, hydroxy ketones, ketone aldehydes, hydroxy acids, ketone acids.

(c) Of the di-secondary alcohols: hydroxy ketones, diketones. (No dibasic acids or alcohol acids,  $C_n$ ), e.g.:



(d) The tri- and polyhydric alcohols are capable of yielding numerous types of products upon oxidation, especially polyhydroxy ketones, polyhydroxy acids, keto-acids, and polybasic acids.

Of all these oxidation products, the most important are the hydroxy acids, the polybasic acids, and the keto-acids.

## IX. HYDROXY MONOBASIC ACIDS AND COMPOUNDS RELATED TO THEM

### A. Monohydroxy Fatty Acids

These compounds may be regarded as monohydroxy derivatives of the fatty acids, e.g.  $\text{OH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , hydroxy-acetic acid, or glycollic acid,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ ,  $\beta$ -hydroxy-propionic acid, or  $\beta$ -lactic acid, &c.

They combine within themselves the **properties of a monobasic acid and of an alcohol**, i.e. they are bi-functional, and consequently are capable of forming derivatives as alcohols, as acids, and as both together.

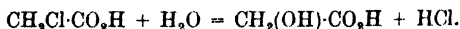
The lowest members of the series are the most important, viz. **glycollic acid** and **lactic acid**, both syrupy liquids which solidify to crystalline masses in the desiccator, and readily give up water to form anhydrides. They cannot be volatilized without decomposition; and are readily soluble in water, and for the most part also in alcohol and ether.

**Formation.**—1. By the regulated oxidation of the glycols. (See summary, p. 236.)

2. From the fatty acids, through their monohalide substitution products, the halogen of these being easily replaced by



hydroxyl, either by means of moist oxide of silver or often by prolonged boiling with water alone:



This reaction is conditioned by the halogen having the  $\alpha$ -position with respect to the carboxyl (cf. pp. 194 and 195).

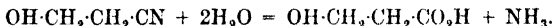
For a reaction of these haloid-substitution products in a different direction, see  $\beta$ - and  $\gamma$ -hydroxy acids.

3. From the aldehydes and ketones containing 1 atom of carbon less, by the preparation of their hydrocyanic acid compounds, **cyanhydrins** (see pp. 148 and 159), and hydrolysis of the latter. Thus, from aldehyde is produced ethylidene cyanhydrin, and from this  $\alpha$ -lactic acid:

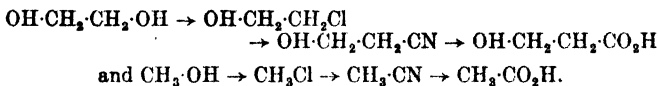


Since the aldehydes and ketones are easily obtained from the corresponding alcohols, this reaction furnishes a means of preparing the acids,  $\text{C}_n\text{H}_{2n}(\text{OH})(\text{CO}_2\text{H})$ , from the alcohols,  $\text{C}_n\text{H}_{2n+1}(\text{OH})$ , i.e. of introducing carboxyl into the latter in place of hydrogen; this is a most important synthesis.

4. From the glycollic cyanhydrins by saponification, e.g.  $\beta$ -lactic acid from ethylene cyanhydrin:



As the cyanhydrins can be readily obtained from the glycols (p. 221), this formation of hydroxy acids represents an exchange of a hydroxyl of the glycol for carboxyl, and is analogous to the formation of acetic acid from methyl alcohol. Thus:

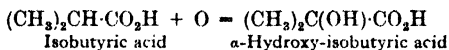


5. By the reduction of aldehydic acids or ketonic acids, e.g. lactic from pyruvic acid (Chap. IX, H.). This reaction corresponds with the formation of the alcohols from the aldehydes or ketones by reduction.

6. By the action of nitrous acid upon amino-acids (see Glycocoll); a reaction analogous to the formation of alcohols from amines (p. 119).

7. Hydroxy acids of the fatty series containing an equal number of carbon atoms result by *direct oxidation*, if a CH

group, i.e. a "tertiary" hydrogen atom, is present in the original acid (R. Meyer, B., 1878, 1283; 1879, 2238):



*Constitution and Isomers.*—As hydroxy compounds of the fatty acids, the acids of the foregoing series can exist in as many modifications as the monohalide fatty acids. Thus there is only one glycollic acid, corresponding with monochloracetic acid, but two lactic acids—corresponding with  $\alpha$ - and  $\beta$ -chloropropionic acids—are possible, and both actually exist; they are designated as  $\alpha$ - and  $\beta$ -hydroxy-propionic acids:

$\text{CH}_3\cdot\text{CHCl}\cdot\text{CO}_2\text{H}$  ( $\alpha$ -chloro-propionic acid).

$\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$  ( $\alpha$ -hydroxy-propionic acid or common lactic acid).

$\text{CH}_3\cdot\text{I}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  ( $\beta$ -iodo-propionic acid).

$\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  ( $\beta$ -hydroxy-propionic acid or  $\beta$ -lactic acid).

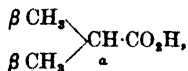
From the two butyric acids can be theoretically derived:

(a) From the normal acid:



an  $\alpha$ -,  $\beta$ -, and  $\gamma$ -hydroxy-butyric acid.

(b) From isobutyric acid:



an  $\alpha$ - and  $\beta$ -hydroxy-isobutyric acid.

*Systematic Nomenclature.*— $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , *Propane-3-ol-1-acid*;  $(\text{CH}_3)_2\text{C}(\text{OH})\cdot\text{CO}_2\text{H}$ , *2-Methyl-propane-2-ol-1-acid*;  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , *Butane-4-ol-1-acid*, &c.

The constitution of these hydroxy acids can often be deduced from their methods of formation. Thus the preparation of common lactic acid from aldehyde,  $\text{CH}_3\cdot\text{CHO}$ , according to method 3, shows that it contains the group  $\text{CH}_3\cdot\text{CH}$ ·, "ethylidene"; it is therefore termed "ethylidene lactic acid". On the other hand, the formation of  $\beta$ -hydroxy-propionic acid from glycol cyanhydrin, according to 4, is a proof of its containing the group  $\cdot\text{CH}_2\cdot\text{CH}_2\cdot$ , "ethylene"; hence the name "ethylene lactic acid".

The constitution can also frequently be deduced from a study of their oxidation products; if they can be oxidized,

for instance, to dibasic acids (which contain two carboxyls) then they must contain a primary alcohol group,  $\cdot\text{CH}_2\cdot\text{OH}$ , since only such a group yields a new carboxyl on oxidation. Ethylene lactic acid is therefore a "primary" alcohol acid. Its isomer, ethylidene lactic acid, is similarly a "secondary" alcohol acid, while  $\alpha$ -hydroxy isobutyric acid is a "tertiary" alcohol acid, i.e. acid and tertiary alcohol at the same time.

*Behaviour.*—1. The bi-functional character of the hydroxy acids will be dealt with more in detail under Glycollic Acid. As acids they form salts, esters, and amides; as alcohols they yield ethers, amines, &c. Of these derivatives the amino-acids,  $\text{NH}_2$  in place of  $\text{OH}$ , are of especial interest. (See Glycocol, p. 243.)

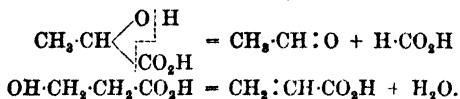
2. The hydroxy acids form different kinds of anhydrides, viz.: (a) as alcohols (see Di-glycollic Acid); (b) one molecule as alcohol forms with a second molecule as acid an ester, with elimination of  $\text{H}_2\text{O}$  (see Glycollic Anhydride); (c) operation *b* is repeated, the first molecule acting as acid, and the second as alcohol (see Glycolide); (d) one molecule loses  $\text{H}_2\text{O}$ , with formation of an "intramolecular" anhydride, a so-called *lactone* (see p. 249).

3. For behaviour upon oxidation see p. 236, and also the individual compounds.

4. Just as the alcohols readily give up water, yielding olefines, so many of the hydroxy acids, especially the  $\beta$ -, can be transferred into unsaturated monobasic acids. (See Hydroacrylic Acid, p. 248.)

5. When warmed with hydriodic acid, the hydroxy acids are reduced to the corresponding fatty acids, just as the alcohols are converted by this reagent into hydrocarbons.

6. When the  $\alpha$ -hydroxy acids are warmed with dilute sulphuric acid, formic acid is produced together with the aldehyde or ketone which would give rise to the acid, according to method 3. The  $\beta$ -hydroxy acids, on the other hand, decompose into water and acids of the acrylic series. Thus:



The  $\alpha$ -,  $\beta$ -,  $\gamma$ -, &c., hydroxy acids also differ from each other in the facility with which they form anhydrides. (See Lactones, p. 249.)

**Glycollic Acid**, *Hydroxy-acetic acid*, *Ethanollic acid*,  $\text{OH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  (*Strecker*, 1848), occurs in unripe grapes, in the leaves of the wild vine, &c.

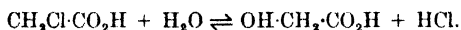
*Formation*.—1. By the oxidation of glycol with dilute  $\text{HNO}_3$  (*Wurtz*).

2. Together with glyoxal and glyoxylic acid, by the oxidation of alcohol with dilute  $\text{HNO}_3$ .

3. By the reduction of oxalic acid with  $\text{Zn} + \text{H}_2\text{SO}_4$ .

4. From formaldehyde synthetically, according to method 3, p. 238.

5. It is usually prepared by boiling chloro-acetic acid with water in the presence of marble, the marble serving to neutralize the  $\text{HCl}$  formed in the reaction (*A.*, **200**, 76):



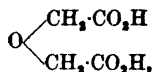
*Properties*.—It forms colourless needles or plates, is readily soluble in water, alcohol, and ether, and melts at  $80^\circ$ . Nitric acid oxidizes it to oxalic acid. The alkaline salts are hygroscopic, the calcium salt and the magnificent blue copper salt are sparingly soluble in water.  $K \times 10^5 = 15.2$ .

*Derivatives*.—(See table, p. 242.) As an acid, glycollic acid forms salts, esters—e.g. **ethyl glycollate**—a chloride, **glycollyl chloride**, and an amide, **glycollamide**, all readily hydrolysed, some of them even on warming with water. All those derivatives still retain their alcoholic character. If, on the other hand, glycollic acid forms derivatives as an alcohol, the properties of the alcoholic derivatives in question are combined with those of an acid, since the hydroxyl of the alcoholic group,  $\cdot\text{CH}_2\cdot\text{OH}$ , enters into reaction, while the carboxyl group remains unchanged. These derivatives are either ethers, such as **ethyl-glycollic acid** (see table), or e.g. amines, such as **glycocoll**, and, as alcoholic derivatives, they are not readily hydrolysed; or they are esters of glycollic acid, as alcohol, e.g. **acetyl-glycollic acid**,  $\text{CH}_2(\text{O}\cdot\text{CO}\cdot\text{CH}_3)\cdot\text{CO}_2\text{H}$ , or **monochloroacetic acid**,  $\text{CH}_2\text{Cl}\cdot\text{CO}_2\text{H}$  (the hydrochloric ester of glycollic acid), and then they are of course saponifiable. These latter compounds still retain their acid character, and, therefore form, on their part, esters, chlorides, and amides, which are also readily hydrolysed. The following table gives a summary of the more important derivatives of glycollic acid:

Acid Derivatives	Alcoholic Derivatives	Mixed Derivatives
HO-CH <sub>2</sub> -CO-ONa Sodium glycollate.		NaO-CH <sub>2</sub> -CO-ONa Di-sodium glycollate. Hygroscopic; decomp. by H <sub>2</sub> O into Na salt and NaOH.
HO-CH <sub>2</sub> -CO-OC <sub>2</sub> H <sub>5</sub> Ethyl glycollate. Liquid, b.-pt. 160°.	OC <sub>2</sub> H <sub>5</sub> -CH <sub>2</sub> -CO-OH Ethyl-glycollic acid. Liquid, b.-pt. 206°.	C <sub>2</sub> H <sub>5</sub> -O-CH <sub>2</sub> -CO-OC <sub>2</sub> H <sub>5</sub> Ethylic ethyl-glycollate. Liquid, b.-pt. 152°.
HO-CH <sub>2</sub> -CO-Cl Glycollyl chloride. Oil; decomposes on volatilizing.	CH <sub>2</sub> Cl-CO-OH Monochloracetic acid.	CH <sub>2</sub> Cl-COCl Monochloracetyl chloride. Liquid, b.-pt. 120°, of suffocating odour.
HO-CH <sub>2</sub> -CO-NH <sub>2</sub> Glycollamide. Crys. M.-pt. 120°; does not form salts with bases.	NH <sub>2</sub> -CH <sub>2</sub> -CO-OH Glycocol. Crys. M.-pt. 236°. Forms salts with acids and bases.	NH <sub>2</sub> -CH <sub>2</sub> -CO-NH <sub>2</sub> Glycocolamide. Crys.

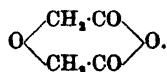
It is easy to see that the corresponding derivatives of the first and second vertical rows are always isomeric.

**Anhydrides of Glycollic Acid.**—1. Glycollic acid can yield different types of anhydrides: (1) the elimination of one mol. of water from the alcoholic hydroxyls of two molecules of the acid produces **diglycollic acid**,



which is obtained by boiling monochloracetic acid with lime. It forms large rhombic prisms, is a dibasic acid, and, as an ether, is not saponified when boiled with alkalis, but is decomposed when heated with concentrated hydrochloric acid to 120°.

2. Diglycollic acid loses water when heated, yielding the **diglycollic anhydride**,



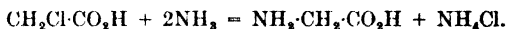
3. **Glycollic anhydride**, OH-CH<sub>2</sub>-CO-O-CH<sub>2</sub>-CO<sub>2</sub>H, is an ester, which is formed when glycollic acid is heated at 100°.

It becomes hydrated again when boiled with water, and may be regarded as an ester derived from glycollic acid acting as an alcohol and as an acid.

4. **Glycolide**,  $\begin{array}{c} \text{CH}_2 \cdot \text{O} \cdot \text{CO} \\ \text{CO} \cdot \text{O} \cdot \text{CH}_2 \end{array}$ , is also an ester anhydride, and is isomeric with 2 (and with fumaric acid). It is formed when sodium bromo-acetate is distilled in a vacuum. Lustrous plates; m.-pt.  $87^\circ$ . It becomes hydrated again when boiled with water.

**Glycocoll** (*Amino-ethane acid*), *glycine*, *amino-acetic acid*,  $\text{NH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$  (*Braconnot*, 1820). This is the simplest representative of the important class of **amino-acids**, so called because they are derived from the fatty acids by the exchange of a hydrogen atom of the hydrocarbon radical for an amino group, e.g.  $\text{CH}_3 \cdot \text{CO}_2\text{H}$ , acetic acid;  $\text{CH}_2(\text{NH}_2) \cdot \text{CO}_2\text{H}$ , amino-acetic acid.

*Formation*.—1. By the action of concentrated ammonia upon monochloroacetic acid:



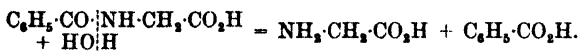
Di- and triglycollamic acids,  $\text{NH}(\text{CH}_2 \cdot \text{CO}_2\text{H})_2$  and  $\text{N}(\text{CH}_2 \cdot \text{CO}_2\text{H})_3$ , are produced at the same time.

$\alpha$ -Chloropropionic acid in like manner yields alanine with ammonia (see Lactic Acid). The method is a general one for the production of amino-acids (*Kolbe*, A., 1860, **113**, 220, cf. J. C. S., 1931, 1391).

2.  $\alpha$ -Amino-acids can also be obtained by reducing  $\alpha$ -keto-acids in presence of excess of ammonia.

3. By boiling glue and other proteins with alkalis or acids, glycocoll and other amino-acids are formed.

4. Together with benzoic acid, by decomposing hippuric acid, i.e. benzoyl-glycocoll, with concentrated hydrochloric acid:



*Properties*.—Glycocoll forms large colourless rhombic prisms, readily soluble in water, but insoluble in absolute alcohol and ether. It has a sweet taste, hence the name "glue sugar" or glycocoll ( $\gamma\lambda\upsilon\kappa\upsilon\varsigma$ , sweet,  $\kappa\acute{o}\lambda\lambda\alpha$ , glue). It melts and decomposes at  $236^\circ$ . Glycocoll, like all the amino-acids, possesses the properties of both an amine and an acid. **Glycocoll hydrochloride**,  $\text{C}_2\text{H}_5 \cdot \text{NO}_2 \cdot \text{HCl}$ , crystallizes in prisms, and the

copper salt, **copper glycocoll**,  $(C_2H_4NO_2)_2Cu + H_2O$ , which crystallizes in blue needles, the latter being obtained by dissolving cupric oxide in a solution of glycocoll. Most of the other amino-acids also form characteristic copper salts of this nature, which serve for their separation. The absence of a free  $CO_2H$  group is indicated by the non-reaction with diazomethane. In neutral solution the amino-acid consists of the neutral ion,  $NH_3^+ \cdot CHR \cdot CO \cdot O^-$ , zwitter ion or hybrid ion.

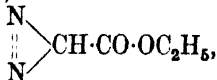
Addition of acid yields the ion  $NH_3^+ \cdot CHR \cdot CO_2H$ , (I), and addition of alkalis the ion  $NH_2 \cdot CHR \cdot CO \cdot O^-$ , (II). (Bio. J., 1930, **24**, 1080.) The free acid is sometimes written as an inner salt  $NH_3^+ \cdot CH_2 \cdot CO \cdot O^-$ . There is only one point at which this salt

or the zwitter ion can exist, and this is termed the isoelectric point. It corresponds with a definite  $p_H$  value, and at this point there is no migration towards either anode or cathode when the amino-acid is placed between electrodes. In more acid solution the complex cation I moves to the anode and in more alkaline solution the anion II towards the cathode. For glycocoll the value for  $p_H$  is 5.96. Glycocoll also yields compounds with salts, and, as an acid, forms an ethyl ester, an amide, &c. (see table, p. 242). When heated with BaO it is decomposed into methyl-amine and  $CO_2$ , while nitrous acid converts it into glycollic acid (the normal reaction of the primary amines). With ferric chloride it produces an intense red, and with copper salts a deep-blue coloration.

Most  $\alpha$ -amino-acids lose  $CO_2$  when heated carefully or with a high boiling solvent, and are readily reduced to amino-alcohols with sodium and alcohol.

For other amino-acids derived from proteins cf. Chap. LXVII, A1.

Ethyl amino-acetate (b.-pt.  $43^\circ/11$  mm.) and nitrous acid yield the valuable **ethyl diazo-acetate**,




from which hydrazine,  $NH_2 \cdot NH_2$ , and its hydrate were first prepared; and from the latter the remarkable compound, hydrazoic acid,  $N_3H$  (*Curtius*).

The reaction is of interest as in the aliphatic series the usual action of nitrous acid is to replace  $NH_2$  by OH.

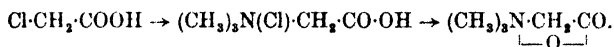
**Alkyl and Acyl Derivatives of Glycocoll:**

Methyl-glycocoll  
or Sarcosine,  
 $\text{CH}_3\cdot\text{NHCH}_2$   
 $\text{CO}\cdot\text{OH}$

Trimethyl-glycocoll  
or Betaïne,  
 $\text{CH}_3\cdot\text{N}(\text{CH}_3)_2$   
 $\text{CO}\cdot\text{O}$  

Acetyl-glycocoll  
or Aceturic Acid,  
 $\text{CH}_3\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$   
 $\text{CO}\cdot\text{OH}$ .


Many of these alkyl derivatives occur as such in natural products, or may be obtained by the decomposition of certain natural compounds. Sarcosine is obtained by the decomposition of the complex natural substances creatine or caffeine. Betaïne occurs in beet-root, and is present in large quantities in the molasses from beet-root sugar (B., 1912, 2248). It crystallizes with  $1\text{H}_2\text{O}$ , which it readily gives up on heating. When heated at  $293^\circ$  betaïne is transformed into the isomeric methyl ester of dimethylaminoacetic acid,  $\text{NMe}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OMe}$ ; at higher temperatures it yields trimethylamine. It has been synthesized by the action of trimethylamine on monochloroacetic acid (B., 1902, 603):



The substituted betaïnes with alkyl in the  $\text{CH}_2$  group readily yield trimethylamine and  $\alpha\beta$ -unsaturated acids when heated, and such acids are often found in nature with tertiary amines.

**Lactic Acids** (*Hydroxy-propionic acids*). Wislicenus, A. 128, 1; 166, 3; 167, 304, 346.)—As has been already mentioned, two isomeric lactic acids are theoretically possible, viz.  $\alpha$ - and  $\beta$ -hydroxy-propionic acids, and both of these are known.

The minute investigation of the different lactic acids has been of very great importance for the development of chemical theory; they were formerly held to be dibasic, and the recognition of their hydroxy-monobasic nature has materially contributed to the acceptance of the theory of atomic linking.

The molecule of  $\alpha$ -hydroxy-propionic acid contains an asymmetric carbon atom,  $\text{CH}_3\cdot\text{CH}$   and hence should exhibit exactly the same kind of isomerism as was met with in the case of active valeric acid (p. 179).

In reality two optically active  $\alpha$ -lactic acids are known, one of which is dextro (*d*), and the other lævo (*l*) rotatory. These two acids are identical in all their properties, with the exception of optical activity. A mixture (or compound) of the



two in equal quantities is optically inactive, and is known as inactive (*dl*) or racemic ( $\tau$ ) lactic acid.

The molecule of  $\beta$ -hydroxy-propionic acid does not contain an asymmetric carbon atom, and hence exists in only one modification, which is optically inactive.

Modes of Formation	Fermentation Lactic Acid	Ethylene-lactic Acid
1. By the regulated oxidation of	$\alpha$ -Propylene glycol, $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\text{OH}.$	$\beta$ -Propylene glycol, $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\text{OH}.$
2. By the exchange of halogen for hydroxyl in	$\alpha$ -Chloro-propionic acid, $\text{CH}_3\cdot\text{CHCl}\cdot\text{CO}\cdot\text{OH}.$	$\beta$ -Iodo-propionic acid, $\text{CH}_2\text{I}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OH}.$
3. By hydrolysis of	Aldehyde-cyanhydrin, $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CN}.$	Ethylene-cyanhydrin, $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}.$
4. By action of nitrous acid upon	Alanine, $\text{CH}_3\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}\cdot\text{OH}.$	
5. By the reduction of	Pyro-racemic acid, $\text{CH}_3\cdot\text{CO}\cdot\text{CO}\cdot\text{OH}.$	
6. By the lactic fermentation of sugar, &c.		

1. ***dl*-Ethylidene-lactic Acid** (*Propane-2-ol-1-acid*), *ordinary fermentation lactic acid*,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$ . Discovered by Scheele, and recognized as hydroxy-propionic acid by Kolbe. Occurs in opium, sauerkraut, and in the gastric juice.

*Preparation*.—By the **lactic fermentation** of sugars, e.g. milk, cane- and grape-sugars by the *lactic bacilli*. The fermentation proceeds best at a temperature of  $45^\circ$ – $55^\circ$  in a nearly neutral solution, in the presence of air, attained by the addition of chalk or zinc-white to the fermenting mixture. The free acid can then be liberated from the zinc lactate by sulphuretted hydrogen. When a non-homogeneous ferment (e.g. decaying cheese) is used, the lactic acid at first produced is readily transformed by other organisms into butyric acid (p. 177).

*dl*-Lactic acid is also produced in large quantity by heating grape- or cane-sugar with caustic-potash solution of suitable concentration:



The same *dl*-acid is formed by mixing equal quantities of the two active modifications. In syntheses the latter are

formed in equal amounts, and hence the inactive acid is obtained.

**Properties.**—It forms a colourless viscous liquid, m.-pt.  $18^{\circ}$  and b.-pt.  $122^{\circ}/15$  mm. soluble in water, alcohol and ether. It is used in tanning and dyeing, to a small extent in pharmacy, and also for the preparation of ethyl and butyl lactates which are used as solvents in Plastics industry. It is a stronger acid than propionic acid due to the  $\alpha$ -hydroxyl group  $K \times 10^5 = 13.8$ . When heated, it is partially converted into the anhydride, lactide,  $C_6H_8O_4$ , and partially into aldehyde, CO, and  $H_2O$ . Similarly it decomposes into aldehyde and formic acid when heated with dilute sulphuric acid to  $130^{\circ}$ , concentrated sulphuric giving rise to carbon monoxide instead of formic acid:



When oxidized, it yields acetic and carbonic acids; hydrobromic acid converts it into  $\alpha$ -bromo-propionic acid, and boiling hydriodic acid into propionic acid itself.

The inactive acid is resolved into the two active modifications by the crystallization of the strychnine salts (*Purdie and Walker*, J. C. S., 1892, 754). When green mould, *Penicillium glaucum*, is sown in a solution of the ammonium salt of the inactive acid, the laevo-acid is assimilated more rapidly than the dextro-, and the solution thus becomes optically active (*Linossier*, B., 1891, 660). A very simple resolution has been accomplished by *Purdie* (J. C. S., 1893, 1143) by crystallizing the zinc ammonium salt,  $ZnC_6H_{10}O_6$ ,  $NH_4C_3H_5O_3$ ,  $2H_2O$ . (Cf. Resolution of Racemic Acid, p. 290.)

A number of well-defined salts are known, e.g. **Calcium lactate**,  $(C_3H_5O_3)_2Ca + 5H_2O$ ; **zinc lactate**,  $(C_3H_5O_3)_2Zn + 3H_2O$ ; **ferrous lactate**,  $(C_3H_5O_3)_2Fe + 3H_2O$ . When sodium lactate is heated with sodium, **di-sodium lactate**,  $CH_3 \cdot CH(ONa) \cdot CO_2Na$ , which is at the same time a salt and an alcoholate, is formed.

The *derivatives* of lactic acid, either as acid or as alcohol, are analogous to those of glycollic acid (see table, p. 242). Thus **ethyl-lactic acid**,  $\alpha$ -ethoxy-propionic acid,  $CH_3 \cdot CH(OC_2H_5) \cdot CO_2H$ , a thick acid liquid which boils almost without decomposition, corresponds with ethyl-glycollic acid; **ethyl lactate**, which can be distilled without decomposition, with ethyl glycollate; **lactamide**,  $CH_3 \cdot CH(OH) \cdot CO \cdot NH_2$ , with

glycollamide; and **alanine**,  $\text{CH}_3\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}\cdot\text{OH}$ , with gly-cocoll.

By the action of  $\text{PCl}_5$ , **lactyl chloride**,  $\text{CH}_3\cdot\text{CHCl}\cdot\text{CO}\cdot\text{Cl}$  (p. 196), is formed; as the chloride of  $\alpha$ -chloro-propionic acid it is decomposed by water, yielding the latter acid and  $\text{HCl}$ .

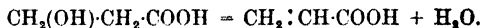
The following anhydrides of lactic acid are known:

(1) **Lactylic acid** or **Lactic anhydride**,  $\text{C}_6\text{H}_{10}\text{O}_5$ , which is analogous to glycollic anhydride, and forms a yellow amorphous mass. (2) **Lactide**,  $\text{C}_6\text{H}_8\text{O}_4$ , analogous to glycolide (plates melting at  $125^\circ$ ). (3) **Dilactic acid**,  $\text{C}_6\text{H}_{10}\text{O}_5$ , the alcoholic anhydride, analogous to diglycollic acid.

2. **d-Ethylidene-lactic acid**, *Sarco-lactic acid*, *para-lactic acid* (*Liebig*). This occurs in the juice of flesh, and is therefore to be found in *Liebig's* extract of meat. Its chemical properties are exactly similar to those of ordinary lactic acid; thus it readily yields lactide or aldehyde. Its salts differ to some extent, however, from those of the latter; thus, the **zinc salt**,  $+ 2\text{H}_2\text{O}$ , is much more easily soluble, and the **calcium salt**,  $+ 4\text{H}_2\text{O}$ , much more sparingly soluble than the corresponding common lactates. Such differences are usually met with between *d*- and *l*-compounds on the one hand, and their *r*-isomeride on the other.

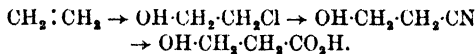
3. **l-Ethylidene-lactic acid** is obtained from the fermentation of cane-sugar by means of the *l-lactic bacillus*. Its salts correspond exactly with the salts of *d*-lactic acid. They have the same formula, same solubilities, &c.

4. **Ethylene-lactic acid** (*Propane-3-ol-1-acid*), *hydraerylic acid* (*Wislicenus*), forms a syrupy mass. It differs from lactic acid (a) by its behaviour upon oxidation, yielding carbonic and oxalic acids, and not acetic; (b) by not yielding an anhydride when heated, but by forming water and the unsaturated acid acrylic acid, hence the name *hydraerylic acid*:



The esters of  $\beta$ -hydroxy acids also lose water, yielding mixtures of  $\alpha\beta$ - and  $\beta\gamma$ -unsaturated esters (*Kon* and *Nargund*, J. C. S., 1932, 2461), depending on the dehydrating agent used; (c) in solubility, and in the amount of water of crystallization of its salts (e.g. zinc salt,  $+ 4\text{H}_2\text{O}$ , very readily soluble in water; calcium salt,  $+ 2\text{H}_2\text{O}$ ). As the OH is in the  $\beta$ -position, it is not so strong an acid as  $\alpha$ -lactic acid ( $K \times 10^5 = 3.1$ ).

It may be synthesized from ethylene by means of the following series of reactions: (a) the addition of hypochlorous acid, (b) conversion of the chlorhydrin into the corresponding nitrile, and (c) hydrolysis, e.g.:



*Le Sueur* (J. C. S., 1904, 827; 1905, 1888) has prepared several hydroxy derivatives of the higher fatty acids, e.g.  $\alpha$ -hydroxy-margaric and  $\alpha$ -hydroxy-stearic acids, and has found that a good yield (35–60 per cent) of an aldehyde can be obtained when the acid is heated to 240°–250°. The molecule of the aldehyde so obtained contains a carbon atom less than the molecule of the hydroxy acid, and water, formic acid, carbon monoxide, and a lactide are obtained as by-products.

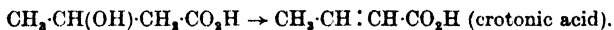
## LACTONES

All hydroxy acids tend to lose water under certain conditions, yielding anhydro-compounds.

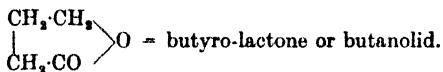
The manner in which this water is eliminated is very different in the various types of hydroxy acids.

1. In the case of the  $\alpha$ -hydroxy acids, 1 or 2 mols. of water are usually eliminated from 2 molecules of the acid, yielding compounds of the type of diglycollic acid, glycollic anhydride, &c.

2. In  $\beta$ -hydroxy acids 1 molecule of water is usually eliminated from 1 molecule of the acid, and an  $\alpha$ - $\beta$ -unsaturated acid is formed, e.g.:



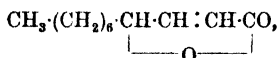
3. In the case of  $\gamma$ -hydroxy acids, e.g.  $\gamma$ -hydroxy-butyric acid,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , 1 molecule of water is eliminated from 1 molecule of the acid, and an inner anhydride or **lactone** is formed,



The formation of such a lactone is characteristic of  $\gamma$ -hydroxy acids. Many of these acids are so unstable in the free state, that when mineral acid is added to their salts the lactones and not the free acids are obtained.

The " $\gamma$ -lactones" are for the most part neutral liquids of faint aromatic odour, readily soluble in alcohol and ether, and distilling without decomposition. In aqueous solution an equilibrium between acid and lactone exists but on the side of the lactone (B., 1918, 430; Z. phys., 1919, **94**, 111). They dissolve in alkalis, yielding the salts of the corresponding hydroxy acids, and form brominated fatty acids with HBr, and amino-acids or amides of  $\gamma$ -hydroxy acids with  $\text{NH}_3$ .

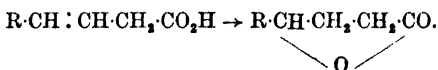
An interesting lactone is *undecalactone*:



obtained by distilling castor-oil with superheated steam, and dehydrating the undecylenic acid with sulphuric acid. It is used for peach, raspberry and strawberry flavourings.

$\delta$ - and  $\beta$ -, but only a few  $\alpha$ -lactones, from  $\delta$ -,  $\beta$ -, and  $\alpha$ -hydroxy acids, are also known. They show marked differences in the ease with which they are formed and in their stability, the  $\gamma$ -lactones being the most stable. (For  $\alpha$ -Lactones see B., 1891, 4070; for  $\beta$ -, B., 1897, 1954, cf. Chap. LVI, A.)

The formation of lactones by warming the isomeric unsaturated acids,  $\text{C}_n\text{H}_{2n-2}\text{O}_2$ , which contain the double bond in the  $\beta$ - $\gamma$  or  $\gamma$ - $\delta$  position, with HBr or with moderately concentrated  $\text{H}_2\text{SO}_4$ , is worthy of note, e.g.:

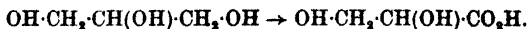


(For details see *Fittig* and his pupils, A., **208**, 37, 111; **216**, 26; **255**, 1, 275; **256**, 50; **268**, 110.)

The reaction is generally regarded as the addition of HBr or  $\text{H}_2\text{O}$  to the double bond, and then the elimination of the Br or OH in the  $\gamma$ -position with the H of the carboxyl group.

## B. Polyhydric Monobasic Acids

Just as glycol on oxidation can yield the monohydroxy monobasic acid, glycollic acid, so the polyhydric alcohols on careful oxidation with nitric acid can yield polyhydroxy monobasic acids, e.g.:



They are usually designated according to the number of alcoholic hydroxyl groups present. This number can be determined by converting the acid, or better, its ester, into the acetyl derivative, and estimating the number of acetyl groups by analysis or by hydrolysis (p. 233).

In none of these acids do we find more than one OH group attached to the same carbon atom. All have the properties of monobasic acids and, in addition, the properties of polyhydric alcohols. Those which contain a hydroxyl group in the  $\gamma$ -position readily yield lactones.

Most of the compounds belonging to this class either crystallize badly or are gum-like. A number of these acids are formed by the cautious oxidation of the sugars or of the unsaturated acids,  $C_nH_{2n-2}O_2$  (see p. 187).

## I. DIHYDROXY MONOBASIC ACIDS

**Glyceric acid** (*Propane-2 : 3-diol-1-acid*),  $OH \cdot CH_2 \cdot CH(OH) \cdot CO_2H$ , is a syrupy liquid which is obtained by the cautious oxidation of glycerol. The molecule contains an asymmetric carbon atom, the artificial acid is optically inactive, but a *d*- and an *l*-modification are known (*Frankland*, J. C. S., 1891, 96).

Various compounds obtained from natural sources are closely related to the dihydroxy acids, viz. serine,  $\alpha$ -amino- $\beta$ -hydroxy-propionic acid, obtained by boiling silk glue with dilute acids; **ornithine**,  $\alpha\delta$ -diamino-valeric acid; and **lysine**,  $\alpha\epsilon$ -diamino-caproic acid, obtained by the hydrolysis of casein.

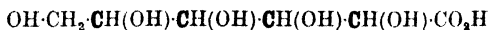
## II. TETRA- AND PENTA-HYDROXY MONOBASIC ACIDS

The tetra- and penta-hydroxy acids, e.g.  $OH \cdot CH_2 \cdot (CH \cdot OH)_3 \cdot CO_2H$  and  $OH \cdot CH_2 \cdot (CH \cdot OH)_4 \cdot CO_2H$ , are of particular importance, on account of their close connexion with the simple sugars. They are obtained either by the cautious oxidation of the corresponding sugars, e.g. by means of bromine water: or by the reduction of the corresponding dibasic acids (saccharic acid, &c.); or, lastly, by the addition of hydrocyanic acid to the polyhydroxy aldehydes or ketones, just as lactic acid is formed from aldehyde. Conversely, the acids, in the form of their lactones, are on the one hand reconverted into the sugars by reduction with sodium amalgam; while, on the other hand, they are oxidized by nitric acid to the corresponding dibasic acids.

The acids are named according to the sugar to which they are related (cf. Chap. XIV, A.):

Arabinose  $\rightarrow$  Arabonic Acid; Glucose  $\rightarrow$  Gluconic Acid.

Some of the acids are known in the form of their lactones only. The phenyl-hydrazones are frequently made use of for their isolation. The penta-hydroxy acid



has 4 distinct asymmetric carbon atoms, and hence exists in many stereo-isomeric forms, viz. the same number as the corresponding aldo-hexoses (Chap. XIV, A.), eight pairs of active isomerides and eight racemic compounds, many of which are actually known.

Three extremely important methods have been employed (mainly by *E. Fischer*) for the preparation of these acids:

1. Oxidation of the corresponding aldehyde (a sugar), e.g. ordinary glucose when carefully oxidized with chlorine- or bromine-water yields *d*-gluconic acid:

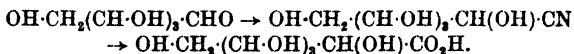


2. From a stereo-isomeric acid by intramolecular transformation under the influence of high temperature, and generally in the presence of an organic base, e.g. *d*-gluconic heated with quinoline and water yields *d*-mannonic; galactonic  $\rightarrow$  talonic.

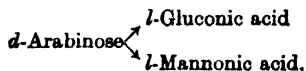
The reaction is a reversible one, and hence the final product is a mixture of the two acids, which can be separated by the difference in solubility of certain of their salts.

The name *epimerization* is given to this reaction which involves an inversion of two groups attached to the  $\alpha$ -carbon atom.

3. The addition of hydrogen cyanide to a polyhydric aldehyde or ketone and subsequent hydrolysis, e.g.:



It is obvious that an additional asymmetric carbon atom is introduced by the addition of the HCN, and thus a mixture of two stereo-isomeric nitriles is formed, and on hydrolysis a mixture of two stereo-isomeric acids, e.g.:

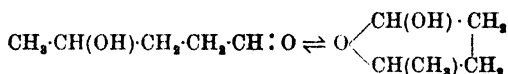


This reaction is somewhat similar to the addition of HCN to acetaldehyde, the main difference is that the original compound is optically active, and hence its molecule is dissymmetric. By the addition of HCN two compounds are obtained, as a rule not in equal amounts, both of which are optically active, but do not stand in the relationship of object to mirror image.

Gluconic acid is largely used in the form of its calcium salt for supplying deficiency of calcium in the human body. It can also be obtained by special bacterial fermentation of glucose.

### C. Hydroxy Aldehydes

Examples are glycollic aldehyde,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}:\text{O}$ , aldol,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CH}:\text{O}$  (see p. 154), and glyceric aldehyde,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}:\text{O}$ . The last-named is contained in glycerose, a product obtained by oxidizing glycerol with bromine water. Alkalis convert it into a mixture of sugars,  $\text{C}_6\text{H}_{12}\text{O}_6$  (see  $\alpha$ -Acrose).  $\gamma$ - and  $\delta$ -hydroxy aldehydes are also known and exist in equilibrium with cyclic isomerides:



(For further examples cf. Monosaccharides, Chap. XIV, A.)

### D. Dialdehydes

**Glyoxal** (*Ethane-dial*),  $\text{CHO}\cdot\text{CHO}$  (*Debus*, 1856), is formed by the careful oxidation of alcohol, or better, of aldehyde; it possesses all the characteristic properties of aldehydes; one molecule of the aldehyde is capable of combining with two of hydrogen cyanide or of sodium hydrogen sulphite.

### E. Hydroxy-ketones

**Acetoin**, methyl  $\beta$ -hydroxyethyl ketone,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}(\text{OH})\cdot\text{CH}_3$ , is the methyl analogue of benzoin (Chap. XXIX). As an  $\alpha$ -hydroxy-ketone it is readily oxidized and also forms solid polymers. **Acetylcarbinol** (hydroxyacetone),  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$  and **Dihydroxyacetone**,  $\text{OH}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$ , are other examples.

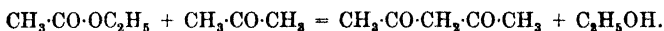


## F. Diketones

The diketones are known as  $\alpha$  or 1:2,  $\beta$  or 1:3, and  $\gamma$  or 1:4-ketones.

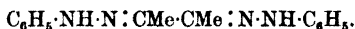
*a. Diacetyl, Butane-dione,  $\alpha$ -diketo-butane*,  $\text{CH}_3\cdot\text{CO}\cdot\text{CO}\cdot\text{CH}_3$ , b.-pt.  $87^\circ\text{--}88^\circ$ , can be prepared by boiling iso-nitrosomethyl-acetone,  $\text{CH}_3\cdot\text{C}(\text{:N}\cdot\text{OH})\cdot\text{CO}\cdot\text{CH}_3$  (from methyl ethyl ketone and nitrous acid), with dilute  $\text{H}_2\text{SO}_4$ , when the oximino group is replaced by oxygen. It is a yellow-green liquid, its vapour having the colour of chlorine, and an odour similar to that of quinone. It is largely used as a butter flavouring and is formed by the action of lactic acid bacteria on butter. Reduction converts it into dimethyl-ketol. Homologues are known.

*$\beta$ . Acetyl-acetone*,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_3$ , formed by the action of aluminium chloride upon acetyl chloride and subsequent decomposition of the aluminium compound, or better by the action of sodium upon a mixture of ethyl acetate and acetone (see Aceto-acetic ester synthesis (this Chap., H2); it is a liquid which boils at  $137^\circ$ .



*$\gamma$ . Acetonyl-acetone, 2:5-diketo-hexane*,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_3$ , may be prepared from monochlor-acetone and ethyl aceto-acetate; also from diaceto-succinic ester. It is a liquid of pleasant odour, and boils at  $188^\circ$ .

As diketones they yield mono- and dioximes, and also mono- and dihydrazones. Such dihydrazones, and also those from the dialdehydes, are termed **osazones**, e.g. **diacetyl osazone**.



Osazones are also formed by the action of phenylhydrazine on polyhydroxy aldehydes or ketones, e.g. glucose and fructose (cf. the phenyl-hydrazine compounds of the carbohydrates).

The diketones show the most varied behaviour on condensation. Alkali and the  $\alpha$ -diketones, with hydrazine and hydroxylamine yield benzene derivatives (Quinone, Chap. XXV, E.); the  $\beta$ -diketones yield pyrazole and isoxo-azole derivatives, and serve for the synthesis of derivatives of quinoline (Chap. XLIV, A2); while the  $\gamma$ -diketones are easily converted into the derivatives of pyrrole, furane, and thiophene, and the

$\delta$ -diketones into derivatives of pyridine (Chap. XLIII, B.) and tetrahydrobenzene.

The constitution of the above compounds is usually deduced directly from their mode of formation, but as certain of them react as tautomeric substances (cf. Ethyl Aceto-acetate) special physical methods have also been used (Chap. LXXI).

### G. Aldehydic Monobasic Acids

**Glyoxalic acid** (*Ethanal acid*), *glyoxylic acid*,  $\text{CHO}\cdot\text{CO}_2\text{H}$ , occurs in unripe fruits such as grapes, gooseberries, &c., and may be prepared by superheating dichloroacetic acid,  $\text{CHCl}_2\cdot\text{CO}_2\text{H}$ , with water, replacement of  $2\text{Cl}$  by  $2(\text{OH})$  and elimination of water. It crystallizes in rhombic prisms, dissolves readily in water, and is volatile with steam. The acid and most of its salts contain one molecule of water of crystallization, which points to the formula  $\text{CH}(\text{OH})_2\cdot\text{CO}_2\text{H}$ , analogous to that of chloral hydrate.

**Glycuronic acid**,  $\text{CHO}\cdot[\text{CH}\cdot\text{OH}]_4\cdot\text{CO}_2\text{H}$ , corresponds in structure with *d*-gluconic acid. The lactone of this acid forms colourless crystals, which melt at about  $175^\circ$ . The acid itself is obtained from saccharic acid by reduction with sodium amalgam. It occurs in many animal organisms and has the property of reacting with many toxic compounds or compounds not readily oxidized in the system and being excreted as such. With alcohols and phenols it forms compounds of the type of  $\alpha$ - and  $\beta$ -glucosides (Chap. XIV, A.).

### H. Monobasic Ketonic Acids

**Ketonic acids** are compounds which contain both a carbonyl and a carboxylic group; they react as acids, and also as ketones; thus, besides being capable of forming salts, esters, &c., they also combine with sodium bisulphite, yield oximes with hydroxylamine hydrochloride (see p. 160), are reduced by nascent hydrogen to hydroxy acids, and so on. The most important members of this class are **pyruvic acid**,  $\text{CH}_3\cdot\text{CO}\cdot\text{CO}_2\text{H}$ , **aceto-acetic acid**,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , and **lævulic acid**,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ .

The three acids mentioned above are examples of the three well-known groups:  $\alpha$ -,  $\beta$ - and  $\gamma$ -ketonic acids or 1 : 2, 1 : 3,

1 : 4-ketonic acids, in which the CO group is in the  $\alpha$ -,  $\beta$ -, or  $\gamma$ -position with respect to the  $\text{CO}_2\text{H}$  group. The structure of any given acid can usually be determined by its method of synthesis or by the hydroxy acid formed on reducing the  $\cdot\text{CO}$  to  $\cdot\text{CH}(\text{OH})$ .

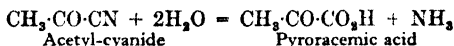
The systematic names of the three acids are pyroracemic = propane-2-one-1-acid, acetoacetic = butane-3-one-1-acid and lævulic = pentane-4-one-1-acid.

The  $\alpha$ - and  $\gamma$ -acids are relatively stable; some can be distilled without undergoing decomposition; but the  $\beta$ -acids are remarkably unstable, and readily lose carbon dioxide, yielding ketones. All the ketonic acids on careful reduction yield hydroxy acids.

Certain of the  $\alpha$ -acids lose carbon dioxide when heated with 10 per cent sulphuric acid at  $150^\circ$  and oxidation of  $\alpha$ -acids with 30 per cent perhydrol yields an acid with one less C atom, thus pyruvic gives acetic.

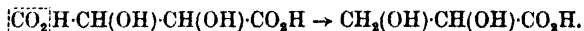
## 1 $\alpha$ -Ketonic Acids

$\alpha$ -Ketonic acids are formed when the acyl cyanides are hydrolysed (*Claisen and Shadwell*, B., 1898, 1023):



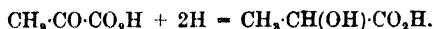
and on reduction yield  $\alpha$ -hydroxy acids.

**Pyruvic** or **pyroracemic acid**,  $\text{CH}_3\cdot\text{CO}\cdot\text{CO}_2\text{H}$ , is a liquid readily soluble in water, alcohol, and ether, boils with slight decomposition at  $165^\circ$ – $170^\circ$ , and smells of acetic acid and extract of beef. It is formed by the dry distillation either of tartaric or of racemic acid, hence its name. In this decomposition carbon dioxide is probably first evolved and the glyceric acid so formed, then loses water, yielding pyruvic acid.



It can also be obtained by the regulated oxidation of the corresponding hydroxy acid, lactic acid,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$ , with perhydrol in the presence of a little ferric acetate (*Fenton and Jones*, J. C. S., 1900, 71). Other oxidizing agents yield oxalic acid.

It has a tendency to polymerize, and nascent hydrogen reduces it to ethylidene-lactic acid:



It is a relatively strong acid owing to the negative nature of the CO group,  $K \times 10^4 = 56$ . It reacts as a ketone with phenyl-hydrazine, hydroxylamine, and hydrogen cyanide.

The **phenyl-hydrazone** crystallizes readily, melts at  $190^\circ$  when quickly heated, and is largely made use of in detecting the acid. The acid also resembles the ketones in the readiness with which it forms condensation products, yielding either benzene derivatives or—in presence of ammonia—those of pyridine.

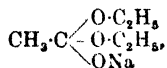
The electrolysis of a concentrated solution of the potassium salt proceeds in the normal manner, the  $\text{CH}_3\cdot\text{CO}\cdot\text{COO}\cdot$  groups formed at the anode yield diacetyl and carbon dioxide (cf. Electrolysis of potassium-acetate solution), but secondary reactions also occur, and acetic acid is formed.

## 2. β-Ketonic Acids

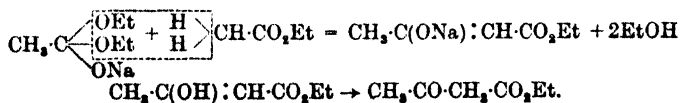
**Claisen** condensation: aceto-acetic and other β-ketonic acids are obtained as esters by the action of sodium or sodium ethoxide on ethyl acetate and its homologues:



According to *Claisen* and *Lowman* (B., 1887, 651; 1893, 2130; 1905, 713; 1908, 1260), the ethyl acetate is first converted by the sodium ethoxide into an additive compound:

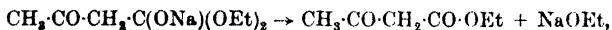


a derivative of ortho-acetic acid (p. 166), which then reacts with another molecule of ethyl acetate:

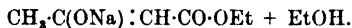


From the sodium salt thus obtained, the aceto-acetic ester can be liberated by acetic acid, probably first as the enolic compound, which is immediately transformed into the ketonic.

Another explanation (*Scheibler*) is that the sodium ethoxide forms the sodium derivative of the enolic form of ethyl acetate, viz.  $\text{CH}_2\text{:C(ONa)(OEt)}$ , which condenses with a second molecule of the ester, the acetyl group becoming attached to the methylene group and the OEt to the second carbon  $\text{CH}_3\text{-CO-CH}_2\text{-C(ONa)(OEt)}_2$ . This product decomposes into ethyl acetoacetate and sodium ethoxide.



which react to give the sodium derivative of the enolic form of ethyl acetoacetate and ethyl alcohol:



(Compare *Michael*, B., 1900, 3731; 1905, 1922; *Stoermer* and *Kippe*, 1905, 1953; 1922, 789.)

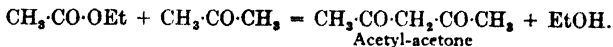
As shown in the above formation of aceto-acetate ester, one molecule of ethyl acetate reacts with a second molecule. Many reactions of an analogous nature can be effected:

(a) With two molecules of the same ester, e.g. ethyl propionate gives ethyl propionyl-propionate,  $\text{CH}_3\text{-CH}_2\text{-CO-CHEt-CO}_2\text{Et}$ ; ethyl methoxyacetate,  $\text{OMe-CH}_2\text{-CO}_2\text{Et}$  gives ethyl  $\alpha$ -dimethoxy-acetoacetate,  $\text{OMe-CH}_2\text{-CO-CH(OMe)-CO}_2\text{Et}$ , and ethyl succinate gives succinilo-succinic ester (Chap. XVII).

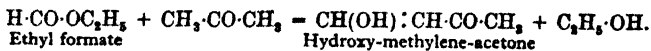
(b) With a mixture of two esters, e.g. ethyl acetate and ethyl oxalate, and EtONa the product is ethyl oxalylacetate (cf. *Dieckmann* B., 1900, 2670):



(c) Esters also readily react with ketones, with the formation of diketones (*L. Claisen*):



When ethyl formate is employed, ketonic aldehydes are not obtained, but their structural isomers, hydroxy-methylene compounds; with acetone, for example, hydroxy-methylene acetone, thus:



This condensation between esters, or between esters and ketones, in the presence of sodium ethoxide is usually known as *Claisen's reaction*, and is of extreme importance as a synthetic process. (For summary see B., 1905, 709.)

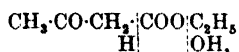
When metallic sodium is used it is essential that small amounts of alcohol should be present in order to yield the sodium ethoxide. Sodamide can replace sodium ethoxide (B., 1905, 693).

**Aceto-acetic acid**,  $\text{CH}_3\text{-CO-CH}_2\text{-CO}_2\text{H}$ , is a strongly acid liquid, miscible with water, and breaking up into acetone and carbon dioxide when warmed. It is prepared by the cautious hydrolysis of its ethyl ester. Its aqueous solution is coloured violet-red by ferric chloride. The Na- or Ca-salt is sometimes contained in urine. Its constitution as acetone-carboxylic acid follows from the products of decomposition.

The ethyl ester, **ethyl aceto-acetate**, or aceto-acetic ester, is prepared by the *Claisen* condensation. It is liberated from the sodium derivative by the addition of acetic acid, and purified by distillation under reduced pressure. It boils at  $181^\circ$ , or at  $71^\circ$  under 12.5 mm. pressure, is only slightly soluble in water, but readily in alcohol and ether, and has a pleasant fruity odour. Ferric chloride colours its aqueous solution violet-red. Extremely characteristic are the products to which it can give rise on hydrolysis.

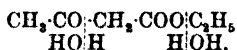
1. *Normal Hydrolysis*.—As an ester, it can be hydrolysed to the corresponding acid and alcohol, viz. aceto-acetic acid and ethyl alcohol. This reaction occurs only when it is extremely carefully hydrolysed in the cold with dilute alkali.

2. *Ketonic Hydrolysis*.—This hydrolysis is best accomplished by the aid of dilute sulphuric acid or baryta water,



the products being acetone, carbon dioxide, and ethyl alcohol. It takes place also when the ester is heated with a little water at  $200^\circ$  (A., 1913, 398, 242).

3. *Acid Hydrolysis*.—This takes place most readily when the ester is heated with concentrated alcoholic potash or soda,



the products being acetic acid and ethyl alcohol.

Ethyl aceto-acetate has been represented by the formula  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ , and undoubtedly numerous arguments can be brought forward in favour of this constitution; e.g. it reacts with sodium bisulphite, with hydrogen cyanide, and with hydroxylamine as a ketone; with nitrous acid it yields an isonitroso compound indicating the presence of the  $\text{CH}\cdot\text{CO}\cdot\text{CH}_2\cdot$  group, and hence should contain the  $\text{C}\cdot\text{CO}\cdot\text{C}$  group; a further argument for the ketonic constitution is to be found in the decomposition of the acid into acetone and carbon dioxide. On the other hand, with ammonia or amines it gives  $\beta$ -amino-, or substituted  $\beta$ -amino-crotonic acids, e.g.  $\text{CH}_3\cdot\text{CH}(\text{NH}_2):\text{CH}\cdot\text{CO}_2\text{H}$ ; with phosphorus pentachloride it yields  $\beta$ -chloro-crotonic acid,  $\text{CH}_3\cdot\text{CCl}:\text{CH}\cdot\text{CO}_2\text{H}$ , and with diazo-methane it gives the methyl ether,  $\text{CH}_3\cdot\text{C}(\text{OMe}):\text{CH}\cdot\text{CO}_2\text{Et}$ ; with acetyl chloride and pyridine it yields  $\text{CH}_3\cdot\text{C}(\text{OAc}):\text{CH}\cdot\text{CO}_2\text{Et}$ , and the sodium derivative with ethyl chloroformate gives  $\text{CH}_3\cdot\text{C}(\text{O}\cdot\text{CO}_2\text{Et}):\text{CH}\cdot\text{CO}_2\text{Et}$ . These latter reactions could be most readily explained by assuming the constitution  $\text{CH}_3\cdot\text{C}(\text{OH}):\text{CH}\cdot\text{CO}_2\text{Et}$ , i.e. ethyl  $\beta$ -hydroxy-crotonate for ethyl aceto-acetate. The ester is thus a typical *tautomeric* substance, reacting as though it possessed two distinct constitutions, and a study of the chemical properties alone will not, as a rule, determine with certainty which of the two is the more probably correct.

The following suggestions have been made to account for the tautomerism:

(a) The ester is really a mixture of the two distinct compounds.

(b) The pure ester is unstable, and although it may have the one constitution, e.g. ethyl aceto-acetate or *ketonic* constitution, in the presence of various reagents it is readily transformed into the isomeric compound with the *enolic* constitution, i.e. ethyl  $\beta$ -hydroxy-crotonate.

(c) According to *Van Laar*, the tautomerism is due to an oscillatory hydrogen atom, which cannot be regarded as permanently attached to C or to O, but as continually oscillating between the two.

A careful examination of the physical constants (cf. Chap. LXXI) has shown that the ester is an equilibrium mixture of the keto and enol forms, but that in the mixture the keto form preponderates. By using *Meyers* bromine method of titration (Chap. LIII, A.) it has been possible to demonstrate the manner

in which the equilibrium is affected by change in conditions, e.g. temperature, solvent, &c.

At room temperature the ordinary ester contains only 7 per cent of enol, and the amount decreases with rise of temperature and increases with different solvents in the order: water 0.4, alcohol acetone, ethyl acetate, benzene, ethyl ether hexane 46.4 per cent under comparable conditions.

Both keto and enol forms have been obtained in a pure state by cooling the mixture in light petroleum to  $-78^{\circ}$ . The keto form melts at  $-39^{\circ}$ , has  $n_D^{10} = 1.4225$ , and does not react with bromine or ferric chloride at low temperatures. The enol has a m.-pt. below the  $-78^{\circ}$ , has  $n_D^{10} = 1.4480$ , and reacts with bromine or ferric chloride even at  $-78^{\circ}$ .

This type of tautomerism is shown by most  $\beta$ -ketonic esters and  $\beta$ -diketones, and is usually termed **Ketoenotic tautomerism** (Chap. LIII, A.).

1. **Ethyl Aceto-acetate as a Synthetical Reagent.**—One atom of hydrogen in the aceto-acetic ester molecule is readily replaceable by metals (*Geuther; Conrad, A., 188, 269*). The **sodio derivative** is formed together with hydrogen on the addition of sodium, and also when an alcoholic solution of the ester is mixed with the calculated amount of sodium ethoxide in absolute alcohol,  $\text{CH}_3\cdot\text{C}(\text{ONa})\text{:CH}\cdot\text{CO}_2\text{Et}$ . This sodio derivative forms long needles or a faintly lustrous loose white mass. The **copper salt** crystallizes in bright green needles.

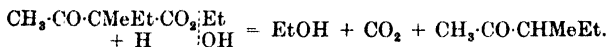
The sodium is readily replaced by alkyl radicals when the sodio derivative is heated with an alkyl bromide or iodide; sodium bromide or iodide is thus formed together with alkylated aceto-acetic esters, which are of great interest in various syntheses, e.g. **ethyl methylacetoacetate**,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}(\text{CH}_3)\cdot\text{CO}_2\text{C}_2\text{H}_5$ , and the corresponding **ethyl- and propyl-acetoacetic esters**, &c. Although the sodio derivative has the enolic structure, i.e. Na attached to O, in the alkyl derivatives, formed by the action of alkyl halides on the metallic compound, the alkyl group is attached to C and not to O (keto structure). In these alkyl compounds the hydrogen atom of the CH group may be again replaced by Na, and this again substituted by alkyl, with the production of dialkylated aceto-acetic esters, e.g. **dimethylacetoacetic ester** or **ethyl dimethylacetoacetate**,  $\text{CH}_3\cdot\text{CO}\cdot\text{C}(\text{CH}_3)_2\cdot\text{CO}_2\text{C}_2\text{H}_5$ ; **methylethylacetoacetic ester**,  $\text{CH}_3\cdot\text{CO}\cdot\text{C}(\text{CH}_3)(\text{C}_2\text{H}_5)\cdot\text{CO}_2\text{C}_2\text{H}_5$ , and so on. The



mono alkyl compounds exhibit keto-enolic tautomerism, but not the dialkyl compounds.

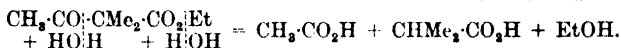
These alkylated aceto-acetic esters exactly resemble the mother substance, especially in the manner in which they can be decomposed by either the "ketonic hydrolysis" or the "acid hydrolysis" (cf. p. 259). The formation of ketone largely predominates when dilute acid is employed, and of fatty acids when concentrated alkali is used.

In the ketonic hydrolysis the alkyl groups introduced are left attached to a carbon atom of the acetone molecule, e.g.:



This affords a very general method for the synthesis of some of the higher ketones.

In the acid hydrolysis the alkyl groups remain attached to the carbon atom, which is united to the carboxylic group, e.g.:

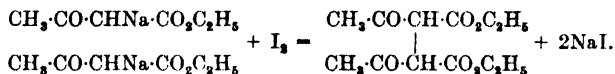


This affords a simple method for synthesizing any mono- or dialkylated acetic acid, e.g.:  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ ;  $\text{C}_2\text{H}_5\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ ;  $(\text{CH}_3)(\text{C}_2\text{H}_5)\text{CH}\cdot\text{CO}_2\text{H}$ ;  $(\text{CH}_3)(\text{C}_3\text{H}_7)\text{CH}\cdot\text{CO}_2\text{H}$ . (Cf. Ethyl malonate synthesis, Chap. X, A.; also *Wislicenus* and his pupils, A., 186, 161.)

2. Acyl groups may be introduced in place of alkyl radicals into aceto-acetic ester by similar methods, e.g. from acetyl chloride, **diaceto-acetic ester**,  $(\text{CH}_3\cdot\text{CO})_2\text{CH}\cdot\text{CO}_2\text{C}_2\text{H}_5$ . The product obtained varies with the conditions. When an acyl chloride reacts with the sodio-derivative of ethyl acetoacetate the chief product is the C-acyl derivative, viz.  $(\text{CH}_3\cdot\text{CO})(\text{R}\cdot\text{CO})\text{CH}\cdot\text{CO}_2\text{Et}$ , but when the free ester is treated with an acyl chloride in the presence of pyridine the isomeric O-acyl derivative is obtained, e.g.  $\text{R}\cdot\text{CO}\cdot\text{O}\cdot\text{C}\cdot\text{CMe}\cdot\text{CH}\cdot\text{CO}_2\text{Et}$ . The O-derivatives, when heated or when warmed with potassium carbonate, are transformed into the isomeric C-compounds.

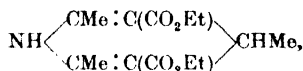
Ethyl chloroformate and the sodio-derivative yield the O-derivative  $\text{CH}_3\cdot\text{C}(\text{O}\cdot\text{CO}_2\text{Et})\cdot\text{CH}\cdot\text{CO}_2\text{Et}$  together with a small amount of the C-derivative, **aceto-malonic ester**,  $(\text{CH}_3\cdot\text{CO})\cdot\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$ ; from monochloroacetic ester,  $\text{CH}_2\text{Cl}\cdot\text{CO}_2\text{C}_2\text{H}_5$ , **aceto-succinic ester**,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}(\text{CH}_2\cdot\text{CO}_2\text{C}_2\text{H}_5)(\text{CO}_2\text{C}_2\text{H}_5)$  may be similarly obtained (see Malonic and Succinic acids, and also the Synthesis of dibasic acids), &c.

3. Iodine acts upon sodio-aceto-acetic ester, yielding **diacetosuccinic ester**:



4. In addition to the above-mentioned simple syntheses, a number of more complex syntheses may be effected by means of ethyl acetoacetate. Many of these lead to the formation of closed-chain compounds, and will be described in connexion with the various groups of ring compounds. The following may be mentioned as the more important:

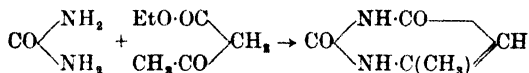
(a) *Hantzsch's* synthesis of pyridine derivatives, e.g. **ethyl dihydrocollidine dicarboxylate**,



by heating ethyl acetoacetate with aldehyde ammonia.

(b) The formation of **oxyuvitic acid** (a benzene derivative),  $\text{C}_6\text{H}_2(\text{CH}_3)(\text{OH})(\text{CO}_2\text{H})_2$ , by the action of chloroform on the sodio-derivative.

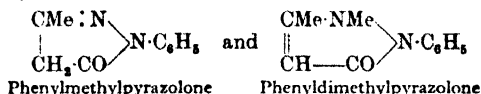
(c) The formation of **methyluracyl** by the condensation of ethyl acetoacetate with urea,



(Synthesis of Uric Acid, Chap. XIII, C.).

(d) The production of **furane** and **pyrrole derivatives** by heating ethyl diacetosuccinate (see Synthesis 3) with acids or with ammonia and amines.

(e) The synthesis of



by the condensation of ethyl acetoacetate with phenylhydrazine and methylphenylhydrazine respectively (Chap. XLII, A.).

**Chlor- and dichlor-aceto-acetic esters**, which are very active chemically, are produced by the replacement of the H of the methylene group by Cl. The two methylene hydrogen atoms are also replaceable by the isonitroso group,  $\text{:N}\cdot\text{OH}$  (by the action of  $\text{N}_2\text{O}_3$ ), and by the imido group,  $\text{:NH}$ .

3.  $\gamma$ -Ketonic Acids

**Lævulic acid**,  $\beta$ -aceto-propionic acid, pentane-4-one-1-acid,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , forms crystalline plates, melts at  $33^\circ$ , and boils at  $239^\circ$ . It is formed by the action of acids upon cane-sugar, lævulose, cellulose, gum, starch, and other carbohydrates, and has also been prepared synthetically. It is employed in cotton printing and for the preparation of anti-thermine, and its methyl and ethyl esters are used as solvents for cellulose nitrates and acetates.

$\gamma$ -ketonic acids do not exist as enols, but when distilled with acetic anhydride yield lactones of a  $\beta\gamma$ -unsaturated acid, e.g. lævulic acid yields  $\text{CH}_3\cdot\text{C}:\text{CH}\cdot\text{CH}_2$



## X. DIBASIC ACIDS

The molecule of a dibasic acid has two carboxylic groups, and can give rise to two series of salts or esters, viz. acid and normal and similarly two chlorides and two amides (cf. p. 268).

A. Saturated Dibasic Acids,  $\text{C}_n\text{H}_{2n-2}\text{O}_4$ , or Acids of the Oxalic Series

Name	Formula	Melting-pt.	$K \times 10^4$
Oxalic .. ..	$\text{CO}_2\text{H}\cdot\text{CO}_2\text{H}$	{ Sublimes 150°-160° }	10 <sup>4</sup>
Malonic .. ..	$\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$	136°	160
Succinic .. ..	$\text{CO}_2\text{H}\cdot[\text{CH}_2]_2\cdot\text{CO}_2\text{H}$	185	6.8
Glutaric .. ..	$\text{CO}_2\text{H}\cdot[\text{CH}_2]_3\cdot\text{CO}_2\text{H}$	97.5	4.8
Adipic .. ..	$\text{CO}_2\text{H}\cdot[\text{CH}_2]_4\cdot\text{CO}_2\text{H}$	151	3.7
Pimelic .. ..	$\text{CO}_2\text{H}\cdot[\text{CH}_2]_5\cdot\text{CO}_2\text{H}$	103	3.4
Suberic .. ..	$\text{CO}_2\text{H}\cdot[\text{CH}_2]_6\cdot\text{CO}_2\text{H}$	140	3.0
Azelaic .. ..	$\text{CO}_2\text{H}\cdot[\text{CH}_2]_7\cdot\text{CO}_2\text{H}$	106.5	2.5
Sebacic .. ..	$\text{CO}_2\text{H}\cdot[\text{CH}_2]_8\cdot\text{CO}_2\text{H}$	127	—

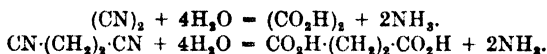
The alkyl substituted malonic and succinic acids have values for  $K$  of much the same order of magnitude as the parent acids.

The above are solid crystalline compounds of strongly acid character, and most of them are readily soluble in water. When heated, they either yield an anhydride, or carbon dioxide is eliminated and a monobasic acid formed; but most of them can be volatilized *in vacuo*.

*Formation*.—1. By the oxidation of the di-primary glycols. (See table, p. 242.)

1a. By the oxidation of hydroxy acids, and, generally, of many complex compounds, such as fats, fatty acids, and carbohydrates.

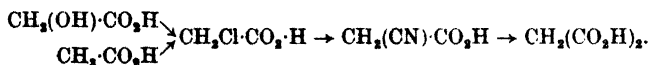
2. By the hydrolysis of the corresponding nitriles; thus, oxalic acid is formed from cyanogen, and succinic acid from ethylene cyanide:



Since ethylene cyanide is a glycol derivative, its conversion into succinic acid represents the synthesis from a glycol of an acid containing two atoms of carbon more than itself, i.e. the exchange of  $2(\text{OH})$  for  $2(\text{CO}_2\text{H})$ , or the indirect combination of ethylene with  $2(\text{CO}_2\text{H})$ .

3. By the hydrolysis of the cyano-fatty acids (p. 195), and consequently from the halogen fatty acids also. Thus chloro- or cyano-acetic acid yields malonic acid;  $\beta$ -iodo- (or cyano-) propionic acid, common succinic acid; and  $\alpha$ -iodo- (or cyano-) propionic acid, methyl-malonic acid.

A dibasic acid can therefore be formed from each hydroxy acid by the exchange of  $\text{OH}$  for  $\text{CO}_2\text{H}$ , or indirectly from a fatty acid by the replacement of  $\text{H}$  by  $\text{CO}_2\text{H}$ . Thus:

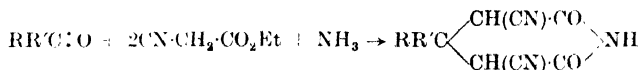


4. The homologues of malonic acid can be prepared from malonic acid itself by a reaction exactly analogous to the aceto-acetic ester synthesis (the "Malonic ester synthesis", p. 272).

5. The dibasic acids are also obtained by means of the aceto-acetic ester synthesis. Aceto-malonic and aceto-succinic acids, which have already been mentioned at p. 262, yield respec-

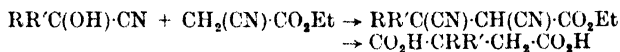
tively malonic and succinic acids by the elimination of acetyl ("acid decomposition").

They can also be synthesized from ketones and ethyl cyanoacetate and ammonia:



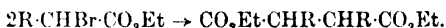
and the cyclic imide on hydrolysis with sulphuric acid yields a  $\beta\beta$ -disubstituted glutaric acid  $CO_2H \cdot CH_2 \cdot CRR' \cdot CH_2 \cdot CO_2H$  (*Kon and Thorpe*, J. C. S., 1919, 693).

An  $\alpha\alpha$ -dialkylated succinic acid is formed by condensing a ketone-cyanhydrin with ethyl cyanoacetate and hydrolysing the product:



(*Higson and Thorpe*, J. C. S., 1906, 1465).

6. A dibasic acid can be synthesized by the elimination of  $Br_2$  from 2 molecules of a bromo-acid in the form of the ester by means of silver,



The yields are poor.

7. Higher homologues are obtainable by the electrolysis of the ethyl potassium salts (p. 268) of the simpler dibasic acids, e.g. adipic acid from potassium ethyl succinate.

The reaction is exactly analogous to the formation of ethane by the electrolysis of potassium acetate. For example, with potassium ethyl succinate the anions  $CO_2Et \cdot \bar{CH}_2 \cdot CH_2 \cdot CO_2$  and kations K are present. When these become discharged at the electrodes during electrolysis, each  $CO_2Et \cdot CH_2 \cdot CH_2 \cdot CO_2$  group splits up into carbon dioxide and the monovalent radical  $CO_2Et \cdot CH_2 \cdot \dot{CH}_2$ . Two such radicals then combine, yielding ethyl adipate,  $CO_2Et \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CO_2Et$ . The potassium formed at the cathode reacts with the water, yielding hydrogen and potassium hydroxide.

The constitution of the acids  $C_nH_{2n-2}O_4$  is, as a rule, very easy to determine from the above-mentioned modes of formation. According to these, one has to decide between the malonic acids proper, i.e. malonic acid and its alkyl derivatives

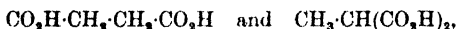
(p. 272), whose two carboxyl groups are both linked to one carbon atom:



and ordinary succinic acid and its homologues, which contain the carboxyls bound to two different carbon atoms.

The bivalent acid residues,  $\text{C}_2\text{O}_2 = \text{oxalyl}$ ,  $\text{C}_3\text{H}_2\text{O}_2 = \text{malonyl}$ , and  $\text{C}_4\text{H}_4\text{O}_2 = \text{succinyl}$ , which are combined with the two hydroxyls, are termed the **radicals of the dibasic acids**, and are examples of bivalent acyl radicals.

*Isomers.*—Isomers of oxalic and malonic acids are neither theoretically possible nor actually known; two succinic acids are known, viz.:



corresponding with ethylene chloride and ethylidene chloride, and known as succinic acid and methylmalonic acid.

Since ethylene cyanide can be prepared from the chloride, the above derivation of ethylene-succinic acid is also an experimental one. This is not the case, however, with the isomeric acid, since, as a rule, when several chlorine atoms are bound to the same carbon atom, as in ethylidene chloride, they cannot be exchanged for cyanogen.

With the higher homologues the number of isomers is larger, e.g. the compound  $\text{C}_3\text{H}_6(\text{CO}_2\text{H})_2$  exists in 4 isomeric forms, viz. glutaric acid  $\text{CO}_2\text{H}[\text{CH}_2]_3\text{CO}_2\text{H}$ ; methylsuccinic acid,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CHMe}\cdot\text{CO}_2\text{H}$ ; dimethylmalonic acid,  $\text{CO}_2\text{H}\cdot\text{CMe}_2\cdot\text{CO}_2\text{H}$  and ethyl malonic acid,  $\text{CO}_2\text{H}\cdot\text{CHEt}\cdot\text{CO}_2\text{H}$ .

The table on p. 264 illustrates two points: (1) The m.-pts. of the acids with an even number of carbon atoms are relatively higher than those of the acids with an odd number. (2) Oxalic acid is an extremely strong acid, i.e. the acid in which the two carboxyl groups are directly united, and the strength of the acid tends to diminish as the chain between the two groups is lengthened. The values  $K \times 10^5$  given are the primary dissociation constants for the first carboxylic group. Each acid has a secondary constant due to the secondary carboxylic group, for oxalic acid the value  $K_2 \times 10^5 = 13.4$ .

*Behaviour.*—Many of the dibasic acids, in the molecules of which the carboxyls are attached to different carbon atoms, yield intramolecular anhydrides by the elimination of a molecule of water from one of the acid. These anhydrides may

be obtained either (1) by heating the acids alone, or (2) more generally by the action of phosphorus pentachloride, acetyl chloride, or carbonyl chloride upon the acids. They recombine slowly with water to form the free acids. This formation of anhydride is favoured by the presence of substituents in the molecule. Malonic and substituted malonic acids lose carbon dioxide and not water when heated.

The elimination of water occurs most readily with succinic and glutaric acids and their substituted derivatives; in fact, with the acids containing a chain of 4 or 5 carbon atoms. This is undoubtedly to be attributed to the spatial relationships of the atoms within the molecule. Assuming that the four valencies of a carbon atom are symmetrically distributed in space (i.e. directed towards the solid angles of a tetrahedron), then it can be readily seen by the aid of models that in acids of the above types the  $\text{CO}_2\text{H}$  groups are brought sufficiently near to one another for water to be eliminated, and for a closed ring to be formed (compare Polymethylene Derivatives).

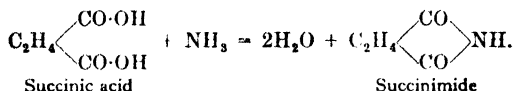
The distance between the carboxylic groups in the different acids has been determined by *Gane and Ingold* (J. C. S., 1928, 1594, 2268), and varies from 1.5 Å for malonic to 16.8 Å for  $n = 7$  in the acids  $\text{CO}_2\text{H}(\text{CH}_2)_n\text{CO}_2\text{H}$ .

The derivatives of the dibasic acids, i.e. their esters, amides, &c., show precisely the same characteristics as the analogous derivatives of the monobasic acids, especially in the readiness with which they are hydrolysed.

#### DERIVATIVES OF DIBASIC ACIDS

Derivatives	Salts	Esters	Chlorides	Amides
Acid.	$\begin{array}{c} \text{CO}\cdot\text{ONa} \\ \text{CO}\cdot\text{OH} \\ \text{Acid sodium} \\ \text{oxalate.} \end{array}$	$\begin{array}{c} \text{CO}\cdot\text{OC}_2\text{H}_5 \\ \text{CO}\cdot\text{OH} \\ \text{Ethyl-oxalic} \\ \text{acid.} \end{array}$	$\begin{array}{c} \text{CO}\cdot\text{Cl} \\ \text{CO}\cdot\text{O}(\text{H}) \\ \text{(only known in} \\ \text{derivatives).} \end{array}$	$\begin{array}{c} \text{CO}\cdot\text{NH}_2 \\ \text{CO}\cdot\text{OH} \\ \text{Oxamic} \\ \text{acid.} \end{array}$
Neutral or normal.	$\begin{array}{c} \text{CO}\cdot\text{ONa} \\ \text{CO}\cdot\text{ONa} \\ \text{Neutral sodium} \\ \text{oxalate.} \end{array}$	$\begin{array}{c} \text{CO}\cdot\text{OC}_2\text{H}_5 \\ \text{CO}\cdot\text{OC}_2\text{H}_5 \\ \text{Ethyl} \\ \text{oxalate.} \end{array}$	$\begin{array}{c} \text{CO}\cdot\text{Cl} \\ \text{CO}\cdot\text{Cl} \\ \text{Oxalyl} \\ \text{chloride.} \end{array}$	$\begin{array}{c} \text{CO}\cdot\text{NH}_2 \\ \text{CO}\cdot\text{NH}_2 \\ \text{Oxamide.} \end{array}$

As in the case of the glycols, complications arise from the formation of mixed derivatives, e.g. partly ester and partly amide, as in the case of ethyl oxamate (p. 270), and also from the fact that many of the acids form imides. Such imides are derived from the hydrogen-ammonium salts of the acids by the elimination of two molecules of water, thus:

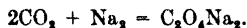


Like the amides they are readily hydrolysed (cf. Succinimide).

**Oxalic acid** (*Ethane diacid*),  $(\text{CO}_2\text{H})_2$ ,  $2\text{H}_2\text{O}$ , is one of the oldest known organic acids, and occurs as its acid potassium salt in many plants, especially in *Oxalis acetosella* (wood-sorrel), and also as the acid or a salt in numerous other plants including rhubarb root.

It may be prepared by a variety of different reactions.

1. By the direct combination of carbon dioxide with sodium at  $360^\circ$ :



2. By quickly heating sodium formate to a high temperature:



3. It is often met with as an oxidation product of relatively complex carbon compounds, e.g. by the oxidation of alcohol by permanganate, and of sugar, starch, wood, &c., by nitric acid. The oxidation of cane-sugar with concentrated nitric acid is often employed for the preparation of pure oxalic acid.

4. On the commercial scale, oxalic acid was manufactured by the fusion of cellulose in the form of sawdust with a mixture of sodium and potassium hydroxides at  $200^\circ$ – $220^\circ$  in flat iron pans. The sodium and potassium oxalates were extracted with water, then precipitated as calcium oxalate, and finally converted into the acid by treatment with the requisite amount of sulphuric acid. This method has become almost completely displaced by method 2.

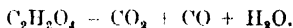
It crystallizes from water with  $2\text{H}_2\text{O}$  in large, transparent monoclinic prisms which slowly effloresce in the air, and readily become anhydrous when carefully heated at  $150^\circ$ ;



the anhydrous acid sublimes unchanged, meets at  $185^{\circ}$  with decomposition ( $\text{CO}_2 + \text{H}\cdot\text{CO}_2\text{H}$  and  $\text{H}_2\text{O} + \text{CO} + \text{CO}_2$ ).

The acid is readily soluble in water, moderately in alcohol, and somewhat sparingly in ether, and cannot be extracted from aqueous solutions by ether or other organic solvent. The aqueous solution decomposes when exposed to light.

Concentrated sulphuric acid decomposes it into carbon monoxide, carbon dioxide, and water:



Oxalic acid is stable towards nitric acid and chlorine, but permanganate of potash or manganese dioxide in acid solution oxidizes it to carbonic acid  $\text{C}_2\text{H}_2\text{O}_4 + \text{O} \rightarrow 2\text{CO}_2 + \text{H}_2\text{O}$ , and it is reduced by nascent hydrogen to glycollic acid.

The strength of an aqueous solution of the acid may be determined by titration with standard alkali, using phenol phthalein as indicator, or by means of standard permanganate in the presence of sulphuric acid.

Its salts are known as **oxalates**. The alkali salts, both acid and normal, are readily soluble in water, the normal sodium salt being the least so. The "**salt of sorrel**" of commerce is a mixture of  $\text{C}_2\text{O}_4\text{HK}$  and a salt,  $\text{KH}_3(\text{C}_2\text{O}_4)_2, 2\text{H}_2\text{O}$  (cf. p. 176). The **calcium salt**,  $\text{C}_2\text{O}_4\text{Ca}, \text{H}_2\text{O}$  (or  $3\text{H}_2\text{O}$ ), is insoluble in water and acetic acid, and serves for the recognition of oxalic acid. **Ferrous-potassium oxalate**,  $(\text{C}_2\text{O}_4)_2\text{FeK}_2 + \text{H}_2\text{O}$ , finds application in photography as a powerful reducing agent (the "**oxalate developer**").

**Ethyl oxalate**,  $(\text{CO}\cdot\text{OC}_2\text{H}_5)_2$ , which can be directly prepared from the anhydrous acid and ethyl alcohol without a catalytic agent, is liquid, while **methyl oxalate**,  $(\text{CO}\cdot\text{OCH}_3)_2$ , is a solid, crystallizing in plates which melt at  $54^{\circ}$ ; both of them possess an aromatic odour, distil without decomposition, and are extremely readily hydrolysed. Partial hydrolysis, with alcoholic potash solution, produces **potassium ethyl-oxalate**,  $\text{COOK}\cdot\text{COOC}_2\text{H}_5$ , from which the free **ethyl-oxalic acid**,  $\text{COOH}\cdot\text{COOC}_2\text{H}_5$ , which is readily hydrolysed, and its chloride, **ethyl-oxalyl chloride**,  $\text{COCl}\cdot\text{COOC}_2\text{H}_5$ , can easily be prepared. Oxalic ester yields, with an excess of ammonia, oxamide, and with one equivalent the mixed derivative, **ethyl oxamate**,  $\text{NH}_2\cdot\text{CO}\cdot\text{CO}\cdot\text{OEt}$ .

**Oxalyl chloride**,  $(\text{COCl})_2$ , has been obtained by the action of

excess of phosphorus pentachloride on ethyl oxalate. It is a liquid, b.-pt.  $70^{\circ}$ , and has a pungent odour (B., 1908, 3558).

**Oxamide**,  $\text{NH}_2\cdot\text{CO}\cdot\text{CO}\cdot\text{NH}_2$ , the normal amide of oxalic acid, is obtained, among other methods, by the distillation of ammonium oxalate, by the partial hydrolysis of cyanogen, but is most readily obtained by the addition of ammonium hydroxide solution to ethyl oxalate. It is a white crystalline powder, is readily hydrolysed, and by the abstraction of water may be converted into cyanogen. When heated it sublimes unchanged.

**Oxamic acid**,  $\text{NH}_2\cdot\text{CO}\cdot\text{CO}\cdot\text{OH}$ , the amic acid corresponding with oxalic acid, is prepared by heating ammonium hydrogen oxalate. It is a crystalline powder, sparingly soluble in cold water, possesses acid properties, and yields salts, esters, &c. It melts and decomposes at  $210^{\circ}$ .

**Ethyl oxamate**, *oxamethane*,  $\text{NH}_2\cdot\text{CO}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , is a crystalline compound, and melts at  $114^{\circ}$ – $115^{\circ}$ . The action of  $\text{PCl}_5$  on this compound is first to form  $\text{NH}_2\cdot\text{CCl}_2\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , **ethyl-oxamine chloride**, which readily loses hydrogen chloride yielding  $\text{NH}\cdot\text{CCl}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$  and finally  $\text{N}\cdot\text{C}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , **ciano-carbonic ester**. Corresponding with oxamide are **dimethyl-oxamide**,  $\text{CH}_3\cdot\text{NH}\cdot\text{CO}\cdot\text{CO}\cdot\text{NHCH}_3$ , and corresponding with oxamethane, **ethyl dimethyl-oxamate**,  $(\text{CH}_3)_2\text{N}\cdot\text{CO}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , both of which were mentioned at p. 117.

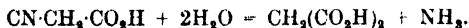
**Oxime**,  $\begin{array}{c} \text{CO} \\ | \\ \text{N} \end{array} \text{NH}$ , is prepared by the action of  $\text{PCl}_5$  upon

oxamic acid. It forms colourless prisms yielding a neutral aqueous solution, which is readily hydrolysed on heating and with ammonia it yields oxamide.

**Cyanogen**,  $\text{N}\cdot\text{C}\cdot\text{C}\cdot\text{N}$ , is the nitrile corresponding with oxalic acid (Chap. XII).

**Malonic acid**, *Propane diacid*,  $\text{CH}_2(\text{CO}_2\text{H})_2$ , occurs in beet-root as its calcium salt, and may be obtained by the following methods:

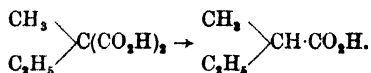
(1) By the oxidation of malic acid by means of chromic acid, hence its name; (2) by the hydrolysis of malonyl-urea (Chap. XIII, C.) (*Baeyer*); (3) by the hydrolysis of cyano-acetic acid, and hence from chloracetic acid:



It crystallizes in large plates, dissolves readily in water,

alcohol, and ether, melts at  $132^{\circ}$ , and decomposes when heated to a slightly higher temperature.

**Ethyl malonate, malonic ester**,  $\text{CH}_2(\text{CO}\cdot\text{OC}_2\text{H}_5)_2$ , is usually obtained by passing hydrogen chloride into a solution of cyanoacetic acid (from chloracetic acid) in absolute alcohol. It is a liquid of faint aromatic odour boiling at  $198^{\circ}$ , and having a remarkable similarity to aceto-acetic ester. Thus the hydrogen of the methylene group, which is attached to two CO groups, is replaceable by sodium; and the resulting sodio-malonic ester readily exchanges the metal for alkyl when treated with an alkyl iodide. By this means the higher homologues of ethyl malonate, e.g. methyl-, ethyl-, propyl-, &c., malonic esters, are obtained. Further, the second hydrogen atom in these can be exchanged in exactly the same manner for sodium and then for alkyl, whereby dialkyl malonic acids are formed. This so-called "malonic ester" synthesis is an important method for the preparation of the higher dibasic acids, being applicable even in complicated cases. (Cf. *Conrad and Bischoff*, A., **204**, 121.) It is also of importance for the preparation of some of the higher fatty acids, as the substituted malonic acids like malonic acid itself, when heated above their melting-points lose carbon dioxide and yield fatty acids:



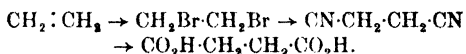
**Malonic anhydride, carbon suboxide**,  $\text{C}_3\text{O}_2$ ,  $\text{O}:\text{C}:\text{C}:\text{C}:\text{O}$ , is formed when malonic acid is heated in a suitable apparatus at  $140^{\circ}$ – $150^{\circ}$ . (*Diels and Wolf*, B., 1907, 355; cf. also 1906, 689; *Staudinger and St. Bereza*, B., 1908, 4461.) The yield is only 10–12 per cent, and acetic acid and carbon dioxide are also formed. It is also formed from the chloride and zinc oxide. It is a colourless liquid, b.-pt.  $+7^{\circ}$ , m.-pt.  $-107^{\circ}$  and  $D_4^0$  1.11. It reacts readily with water, hydrogen chloride, dry ammonia, and aniline, yielding respectively malonic acid, malonyl chloride, malonamide, and malonanilide. It is stable at low temperatures, but decomposes rapidly at  $100^{\circ}$ .

**Malonyl chloride**,  $\text{CH}_2(\text{COCl})_2$ , from the acid and thionyl chloride, is a colourless liquid, b.-pt.  $58^{\circ}/27$  mm. The half chloride  $\text{COCl}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , obtained when less thionyl chloride is used, melts at  $65^{\circ}$ , and on keeping yields acetyl chloride and  $\text{CO}_2$ .

The amide, m.-pt. 168°-170°, is readily formed by the action of ammonia on ethyl malonate, whereas dialkylated malonic esters do not react in this way.

**Succinic acid**, *Butane diacid*, *ethylene-succinic acid*, *symmetrical ethane-dicarboxylic acid* (from *succinum* = amber),  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ . This acid has been known for a long time; its composition was determined by *Berzelius*. It exists in amber, in various resins and lignites, in many *Compositæ*, in *Papaveraceæ*, in unripe wine grapes, urine, blood, &c.

It may be obtained by most of the general methods described on p. 265, e.g. 1. By the hydrolysis of ethylene cyanide. This is an extremely important method, as it affords a synthesis of succinic acid and also establishes its constitution, since it can be shown that in ethylene dibromide the two bromine atoms are attached to distinct carbon atoms:



2. From  $\beta$ -iodo-propionic acid by conversion first into  $\beta$ -cyano propionic acid and subsequent hydrolysis.

3. By the reduction of fumaric and maleic acids,  $\text{CO}_2\text{H}\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ .

4. By heating its hydroxy acids, malic or tartaric, with hydriodic acid:

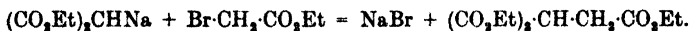


5. It may also be obtained by the fermentation of the salts of these hydroxy acids by means of certain micro-organisms, e.g. certain species of bacteria or yeasts.

It is also formed in small quantities as a by-product in the alcoholic fermentation of sugar, and by the oxidation of fats, fatty acids, and paraffins by means of nitric acid.

It is usually prepared from calcium malate according to 5, or by the distillation of amber.

6. It may also be synthesized from ethyl malonate. The sodio-derivative of this ester reacts not merely with alkyl iodides or bromides, but also with the esters of halide fatty acids, e.g. ethyl bromoacetate.



The product is **ethyl ethane-tricarboxylate**, and when this is hydrolysed, alcohol, carbon dioxide, and succinic acid are

formed. This method is of general interest, as various substituted succinic acids may be synthesized by this method. In place of sodio-ethyl malonate, the sodio-derivatives of esters of mono-substituted malonic acids may be used, and in place of ethyl bromo-acetate the esters of other halogen fatty acids, e.g. ethyl iodo-propionate or ethyl bromo-valerate. It has been shown (*Bone and Sprankling*, J. C. S., 1899, 839) that better yields can be obtained by using ethyl cyano-acetate and its derivatives in place of ethyl malonate and its derivatives.

*Properties.*—It crystallizes in monoclinic prisms or plates with an unpleasant faintly acid taste, is readily soluble in water, melts at  $185^{\circ}$ , and boils at  $235^{\circ}$ , but is at the same time partially converted into its anhydride. (For its electrolysis see pp. 34 and 266.) Is very stable towards oxidizing agents.

Of the salts of succinic acid, the **basic ferric salt**, obtained by the addition of a ferric salt to ammonium succinate, is used in analysis for the separation of the ferric and aluminic radicals. The **calcium salt** is soluble in water.

The derivatives of succinic acid correspond closely with those of oxalic, e.g. **succinamic acid**,  $\text{NH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OH}$ , is analogous to oxamic acid, and **succinamide**,  $\text{NH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}_2$ , m.-pt.  $243^{\circ}$  to oxamide. There also exists, as in the case of other dibasic acids, an imide,

**succinimide**,  $\text{C}_2\text{H}_4 \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{NH}$ , m.-pt.  $124^{\circ}$ . The latter crystallizes

in rhombic plates, and is formed by heating ammonium hydrogen succinate. The basic properties of the NH are so modified by the two carbonyl groups of the acid radical that the imido-hydrogen is replaceable by metals, such as K, Ag, &c. **Succinyl chloride** reacts as though it were **dichloro-butyro-lactone**,

$\text{C}_2\text{H}_4 \begin{array}{c} \diagup \text{CCl}_2 \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{O}$ . It is a colourless liquid boiling at  $190^{\circ}$ , and

is obtained by the action of phosphorus pentachloride (2 mols.) on the acid, or of 1 mol. on the anhydride. In many of its properties it resembles the acid chlorides, but on reduction yields **butyro-lactone**; with benzene and aluminium chloride

it yields mainly  $\gamma$ -**diphenyl-butyro-lactone**,  $\text{C}_2\text{H}_4 \begin{array}{c} \diagup \text{CPh}_2 \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{O}$ ,

and with zinc-ethyl,  $\gamma$ -diethyl-butyro-lactone. With  $\text{NH}_3$  it yields but little amide, but with aniline gives the normal anilide (cf. *Auger*, *Annales*, 1891 (vi), **22**, 326; *Morell*, *J. C. S.*,

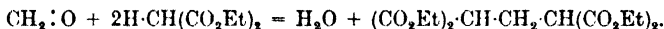
1914, 1733). **Succinic anhydride**,  $\text{C}_2\text{H}_4 \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{O}$ , is best

obtained by the action of acetic anhydride on the acid. It crystallizes in glistening plates, melts at  $120^\circ$ , and distils without decomposition. It slowly combines with water, yielding the acid; more readily with alkalis, and also with alcohols at a higher temperature, yielding the **acid esters**, e.g.  $\text{HO}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OEt}$ . This is the most convenient method for the preparation of acid esters. The other methods sometimes employed are: (a) the partial hydrolysis of the neutral ester, and (b) the partial esterification of the acid by means of very dilute solution of hydrogen chloride in the requisite alcohol (*Bone*, *Sudborough*, and *Sprankling*, *J. C. S.*, 1904, 534).

Sodium reacts with ethyl succinate, yielding **ethyl succinylsuccinate**, a compound related to benzene (Chap. XVII, F.).

The *s*-**dimethyl**- and *s*-**dibromo-succinic acids**,  $\text{CO}_2\text{H}\cdot\text{CHBr}\cdot\text{CHBr}\cdot\text{CO}_2\text{H}$ , occur in the same number of stereoisomeric modifications as the tartaric acids (p. 285).

**Glutaric acid**, *Pentane diacid*,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , may be obtained from glutamic acid (p. 284), and also by condensing formaldehyde with ethyl malonate in the presence of a small amount of diethylamine:



This is a further example of the readiness with which aldehydes condense with compounds containing a methylene group adjacent to carbonyl or negative groups. The product, **ethyl propane-tetracarboxylate**, on hydrolysis yields ethyl alcohol, carbon dioxide, and glutaric acid. The last crystallizes in prisms, melts at  $97^\circ$ , is readily soluble in water, and yields an **anhydride**, an **imide**, &c. The imide can be obtained when piperidine is oxidized with hydrogen peroxide, and when distilled with zinc dust yields a small amount of pyridine.

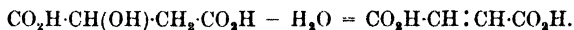
Isomeric with glutaric acid is **methyl-succinic** or **pyro-tartaric acid**,  $\text{CO}_2\text{H}\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , an acid closely resembling succinic acid, and obtained by dry distillation of tartaric acids.

The  $\beta\beta$ -dialkylglutaric acids have much higher dissociation constants ( $K_1 \times 10^4 = 2$  to 3) than  $\beta$ -monoalkyl acids (0.6 – 0.7), J. C. S., 1939, 446).

## B. Unsaturated Dibasic Acids

The unsaturated acids stand in the same relation to the saturated dibasic acids as acrylic acid does to propionic. As dibasic acids they yield derivatives analogous to those of oxalic acid, while as unsaturated compounds each molecule possesses, in addition, the property of combining with two atoms of hydrogen or halogen, or with one molecule of halogen hydride.

*Common Methods of Formation.*—1. By the elimination of water from the hydroxy-dibasic acids. Thus malic acid when distilled yields water and maleic anhydride, which volatilizes, and also fumaric acid, which remains behind:



The actual product obtained by the elimination of water from malic acid varies considerably with the conditions of the experiment. Thus, when malic acid is maintained at a temperature of 140°–150° for some time, the chief product is fumaric acid; when the malic acid is rapidly heated at a higher temperature, maleic anhydride is largely formed.

Citric acid yields, in a similar way,  $\text{CO}_2$ ,  $\text{H}_2\text{O}$ , itaconic acid,  $\text{CH}_2:\text{C}(\text{CO}_2\text{H})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , and citraconic anhydride (methylmaleic anhydride).

2. By the separation of halogen hydride from the monohalide derivatives of succinic acid and its homologues, e.g. monobromo-succinic acid yields fumaric, thus:

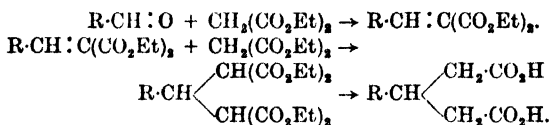


3. Fumaric acid has been prepared synthetically from acetylene di-iodide, just as succinic acid has been from ethylene dibromide.

4. For syntheses from aromatic aldehydes cf. Chap. XXVI, A2.

Ethyl malonate reacts with an aliphatic aldehyde yielding

an unsaturated ester, but this can react with a second molecule of the malonic ester (*Michael* addition), yielding the ester a tetracarboxylic acid which on hydrolysis gives a  $\beta$ -alkylglutaric acid:



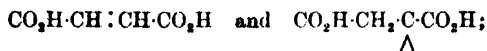
**Constitution.**—The acids of this series may be regarded as dicarboxylic acids of the olefines, e.g. fumaric and maleic acids,  $\text{C}_2\text{H}_2(\text{CO}_2\text{H})_2$ , as those of ethylene. Their mode of formation 1 corresponds exactly with the production of ethylene from alcohol, or with that of acrylic from ethylene lactic acid, while 2 agrees with that of ethylene from ethyl iodide.

**Maleic acid** (*cis-Butene diacid*),  $\text{CO}_2\text{H}\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ , crystallizes in large prisms, possesses a grating, nauseous acid taste, and is very readily soluble in cold water. It distils unchanged, excepting for partial transformation into maleic anhydride. It is conveniently prepared by heating the acetyl derivative of malic acid (this Chap., C.), or from fumaric acid and  $\text{POCl}_3$ .

**Fumaric acid** (*trans-Butene diacid*),  $\text{C}_2\text{H}_2(\text{CO}_2\text{H})_2$ , crystallizes in small prisms with a strong, purely acid taste, and is almost insoluble in cold water. It does not melt, but sublimes at about  $200^\circ$  with formation of maleic anhydride. It occurs in *Fumaria officinalis*, various fungi, truffles, Iceland moss, &c., and is obtained from maleic acid either by prolonged heating of the latter at  $130^\circ$ , or by the action upon it of hydrobromic or other acids.

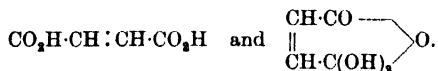
Both acids are converted into the corresponding esters when their silver salts are heated with alkyl iodide. Ethyl malcate is changed into ethyl fumarate when warmed with iodine, and the latter ester is formed by saturating an alcoholic solution of maleic acid with dry hydrogen chloride.

**Isomerism of Fumaric and Maleic Acids.**—At one time the acids were thought to be polymeric or even structurally isomeric, and *Fittig* suggested the formulæ:





but isomerism of this type is impossible, since both acids when oxidized yield one or other of the tartaric acids  $\text{CO}_2\text{H}\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$ . *Anschtütz* suggested the formulæ



Such a formula as the latter is not at all probable, as in this case maleic acid, which is the stronger acid ( $K_1 \times 10^4 = 150$ , and for fumaric  $K_1 \times 10^4 = 10$ ), would not possess a carboxylic, but merely a hydroxy-lactone structure (*Wegscheider*, B., 1903, 1543). This formula is also found to be quite untenable when the products of bromination and of oxidation are considered.

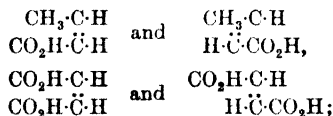
The fact that the two acids are structurally identical, and must both be represented as ethylene dicarboxylic acids, is now generally recognized, and the conclusion is largely based on the following facts: (1) Both acids when reduced with sodium amalgam yield ordinary succinic acid. (2) Both acids combine with hydrogen bromide, yielding the same bromo-succinic acid. (3) Both acids combine with water at moderate temperatures, yielding the same malic acid. In most of these additive reactions the maleic acid reacts somewhat more readily than the fumaric, and is at the same time partially transformed into fumaric. (4) When carefully oxidized, the two acids yield stereo-isomeric tartaric acids, maleic being transformed into meso-tartaric, and fumaric into racemic acid. (5) Similarly, on addition of bromine they yield stereo-isomeric dibromo-succinic acids.

As the two acids are structurally identical, the isomerism can only be accounted for by a different spatial relationship of the atoms within the molecule. The stereo-isomerism of these unsaturated compounds is quite distinct from that of the saturated compounds, such as lactic and tartaric acids. In saturated compounds where two C atoms are united by a single bond, there must be free rotation around the axis represented by the bond, otherwise the number of isomerides  $\text{Ca b c}\cdot\text{C d e f}$ , or even  $\text{Ca a b}\cdot\text{Ca a b}$ , would be much greater than what is actually found. When, however, the two carbon atoms become united by a so-called double bond, free rotation is completely prevented, and the centres of gravity of the two

C atoms and of the four substituents all lie in the same plane, viz. the plane of the paper.



No stereo-isomerism is possible with such a compound, nor yet with any compound in which the 2 radicals attached to the one carbon atom are the same, e.g.  $\text{CH}_2:\text{CCl} \cdot \text{CO}_2\text{H}$ ; but immediately each carbon atom has 2 different radicals attached to it, isomerism is theoretically possible, e.g. crotonic acid,  $\text{CH}_3 \cdot \text{CH}:\text{CH} \cdot \text{CO}_2\text{H}$ , and maleic acid,  $\text{CO}_2\text{H} \cdot \text{CH}:\text{CH} \cdot \text{CO}_2\text{H}$ , viz.:



and similarly for oleic and elaidic acids, erucic and brassidic acids, cinnamic and allocinnamic acids and its derivatives, and also for numerous other compounds.

As the centres of gravity of the carbon atoms and of their substituents all lie in one plane, the molecules are not dissymmetric, and therefore possess no optical activity, and cannot be resolved into optically active components.

A few exceptions to this generalization were at one time supposed to exist. Thus it was stated that an optically active solution of citraconic acid,  $\text{CO}_2\text{H} \cdot \text{CMe}:\text{CH} \cdot \text{CO}_2\text{H}$ , was obtained by the growth of certain fungi on the liquid. *Le Bel* (1894) was able to show that by the addition of water to the unsaturated acid, methyl-malic acid is formed and is then attacked by the organism. Similarly, the slight activity attributed to cinnamene, chlorofumaric, and chloromaleic acids has been shown to be due to small amounts of impurities (*Perkin*, J. C. S., 1888, 695). *Erlenmeyer* still claims to have obtained optically active cinnamic acids (cf. Chap. XXVI, A2).

The two isomerides are not so closely related to one another as *d*- and *l*-valeric acids, or as *d*- and *l*-tartaric acids; as a rule, they differ entirely as regards their ordinary physical properties, e.g. crystalline form, solubility, melting-point, water of crystallization, dissociation constant, &c., and in many cases considerable differences in chemical properties are met with, e.g. maleic acid yields an anhydride and fumaric acid does not.

As a rule, one of the isomerides is less stable than the other, and under suitable conditions, e.g. influence of (a) heat, (b) light, (c) chemical reagents, especially small amounts of halogens or halogen hydracids, the labile compound is transformed into the stable. With certain pairs of isomerides the transformation is mutual, so that whichever of the two we start with we obtain, under the conditions enumerated above, a mixture of the two in chemical equilibrium.

As examples of the transforming action of heat we have the following: Fumaric  $\rightarrow$  maleic; allocinnamic  $\rightarrow$  cinnamic; angelic  $\rightarrow$  tiglic, and either chloro-fumaric,  $\text{CO}_2\text{H}\cdot\text{CCl}:\text{CH}\cdot\text{CO}_2\text{H}$ , or chloro-maleic acid heated separately yields a mixture of the two. The effect of exposure to sunlight is often identical with the action of heat, but not always so, e.g. ethyl benzyl-

aminocrotonate,  $\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \text{C}:\text{CH}\cdot\text{CO}_2\text{Et} \\ \diagup \\ \text{CH}_2\text{Ph}\cdot\text{NH} \end{array}$ , exists in two

stereo-isometric modifications melting at  $79^\circ$  and  $21^\circ$ ; the effect of heat is to transform the higher melting ester into the lower melting, and the effect of sunlight is the exact opposite. As examples of the influence of chemicals, we have the action of small amounts of nitrous acids in transforming oleic into elaidic and erucic into brassidic acids. Similarly, small amounts of bromine will transform dimethyl maleate into dimethyl fumarate.

Ultra-violet light, on the other hand, by the addition of energy, transforms the stable into the labile modification, e.g. cinnamic acid into allocinnamic acid, and often the most convenient method of preparing the labile form is to expose the stable compound to the action of the rays from a quartz mercury vapour lamp (*Stoermer*, B., 1909, 4865; 1911, 637; 1912, 3099; 1914, 1786, 1795, 1863; A., 1915, 409, 13).

*Skraup* has shown that either sulphur dioxide or hydrogen sulphide alone is unable to transform maleic into fumaric, but that a mixture of the two will bring about the transformation. The chemical reaction between the  $\text{H}_2\text{S}$  and  $\text{SO}_2$  may be regarded as a type of detonator which starts the transformation in the maleic acid. All chemical reactions, however, cannot act in the same manner as catalysts. The salts of maleic acid, e.g. copper maleate, when decomposed by hydrogen sulphide yield fumaric acid or a mixture of fumaric and maleic acids, although, as stated above, the sulphide itself is incapable of

transforming free maleic acid into fumaric. Sodium thiosulphate alone brings about the isomeric change, and potassium in dry ether isomerizes methyl maleate. A small amount of a primary or secondary amine, e.g. piperidine, brings about the change in a few seconds (J. C. S., 1930, 213).

The exact method of transformation is not known. It may be (a) that the two radicals attached to the one carbon atom actually exchange positions directly; (b) the two carbon atoms may only be in a state of strain, and under the influence of light, heat, &c., a rotation through an angle of  $180^\circ$  may occur; or (c) in changes brought about by chemical agents the agent employed may first form an additive compound and then be subsequently removed, but this view has been shown to be impossible in many cases by *Anschütz*, *Fittig*, and *Michael*. *Terry* and *Eichelberger* (J. A. C. S., 1925, 1067, 1402) suggest the change of the covalent double linking to a semipolar linking.

The system of nomenclature adopted to distinguish between the two isomerides is to term the compound in which two similar substituents are on the same side of the molecule the *cis* compound, and the isomeride in which the two similar radicals are on opposite sides of the molecule the *trans*:



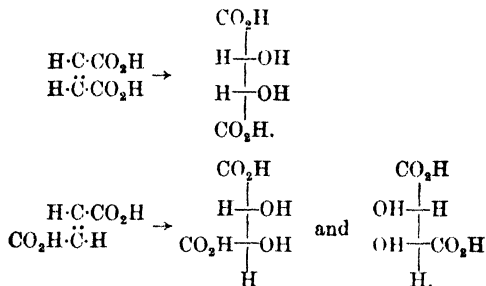
In cases where it has not been found possible to ascertain which of the two known compounds has the *cis* configuration and which the *trans*, the ordinary name is given to the one and the prefix *iso*, or better, *allo*, to the other, e.g. crotonic and isocrotonic acids, cinnamic and allocinnamic acids.

*Determination of Configuration.*—In the case of fumaric and maleic acids this has been accomplished with a considerable degree of certainty. The arguments used for the *cis* configuration of maleic and the *trans* configuration of fumaric are briefly: (a) Maleic acid when heated, or treated with dehydrating agents, readily yields an anhydride (cf. Succinic

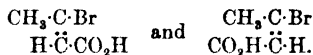
anhydride),  $\begin{array}{c} \text{CH}\cdot\text{CO} \\ \parallel \\ \text{CH}\cdot\text{CO} \end{array} \text{O}$ , which can combine with water to

re-form maleic acid. Fumaric acid yields no distinct anhydride of its own. (b) Maleic acid when oxidized yields meso-tartaric

acid, whereas fumaric acid yields racemic acid (see p. 289):



The configurations of other pairs of olefine stereo-isomerides have not been determined with the same degree of certainty, and many of the methods described in text-books as being available for this purpose cannot be relied on, e.g. of two stereo-isomeric  $\alpha$ - or  $\beta$ -halogenated compounds, the one which has the halogen in the *cis*-position with respect to a hydrogen atom will lose halogen hydracid more readily under the influence of alkali, e.g.:



In many cases it is probable that exactly the reverse holds good.

Similarly it was assumed that by the addition of hydrogen, chlorine, bromine, iodine, or their hydracids to an acetylene derivative, the addenda, e.g. two bromine atoms or one bromine and one hydrogen, assume the *cis* positions in the olefine compound formed. It has been conclusively proved that acetylene-dicarboxylic acid with halogen hydracids yields mono-halide derivatives of fumaric and not maleic acid (*Michael*, J. pr., 1892, 46, 210; 1895, 52, 352). According to *Garner* (C. N., 1919, 119, 16), *trans* addition and *trans* elimination are the rule and not the exception, and can be accounted for by *Bohr's* theory of the arrangement of the atoms and electrons within the molecule.

**Acetylene-dicarboxylic acid**, *Butine diacid*,  $\text{CO}_2\text{H} \cdot \text{C} \equiv \text{C} \cdot \text{CO}_2\text{H}$ , a type of an acetylenic acid, is obtained by the elimination of two molecules of hydrogen bromide from one of dibromo-succinic acid. It is a dibasic acid, and also an unsaturated

compound, but does not yield metallic derivatives of the type of silver acetylene. It readily loses carbon dioxide, yielding propargylic acid,  $\text{CH}::\text{C}\cdot\text{CO}_2\text{H}$ . **Diacetylene-dicarboxylic acid**,  $\text{CO}_2\text{H}\cdot\text{C}::\text{C}\cdot\text{C}::\text{C}\cdot\text{CO}_2\text{H}$ , and **tetracetylene-dicarboxylic acid**, *Decatetrine diacid*,  $\text{CO}_2\text{H}\cdot\text{C}::\text{C}\cdot\text{C}::\text{C}\cdot\text{C}::\text{C}\cdot\text{C}::\text{C}\cdot\text{CO}_2\text{H}$ , have been prepared by *Baeyer* (B., 1885, 678 and 2269).

### C. Hydroxy Dibasic Acids

1. **Tartronic acid**, *Propanol diacid*, *hydroxy-malonic acid*,  $\text{OH}\cdot\text{CH}\cdot(\text{CO}_2\text{H})_2$ , forms large prisms ( $+\frac{1}{2}\text{H}_2\text{O}$ ), and is easily soluble in water, alcohol, and ether. It cannot be distilled unchanged, since it breaks up on heating into carbon dioxide and glycolide. As hydroxy-malonic acid it may be prepared by the action of moist silver oxide on chloromalonic acid. It may also be obtained by the reduction of the corresponding ketonic acid, mesoxalic acid,  $\text{CO}(\text{CO}_2\text{H})_2$ , and also by the oxidation of glycerol with permanganate.

2. **Malic acid**, *Butanol diacid*, *hydroxy-succinic acid*,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$  (*Scheele*, 1785), is very widely distributed in the vegetable kingdom, being found in unripe apples, sorb-apples, grapes, barberries, mountain-ash berries, quinces, &c.

Some of the simpler methods of formation are quite analogous to those employed in the case of hydroxy monobasic acids, e.g. (1) by the action of moist silver oxide on bromo-succinic acid; (2) by the reduction of tartaric or racemic acid with HI, and of oxal-acetic acid (p. 258 and this Chap., F.) with sodium-amalgam; (3) by the action of nitrous acid on the corresponding amino-acid, aspartic acid; and (4) it is manufactured by the addition of water to maleic acid by heating with steam under pressure.

It crystallizes in hygroscopic needles, is readily soluble in water and alcohol, but only sparingly in ether. It melts at  $100^\circ$ , and when it is distilled, maleic anhydride passes over and fumaric acid remains in the retort (p. 276).  $K \times 10^5 = 40$ .

The molecule of malic acid contains an asymmetric carbon atom, and thus the acid should exist in two optically active and a racemic modification. The acid obtained from natural sources, *l*-malic acid, is lævo-rotatory in dilute solution, but the rotation diminishes as the concentration increases. With a

34 per cent solution at  $20^{\circ}$  no optical activity is shown, and with more concentrated solutions dextro-rotation is exhibited. The acid obtained synthetically is optically inactive and constitutes the racemic form, and it has been resolved into optically active modification by the usual methods (p. 290) (B., 1898, 528).

The alkali salts and the acid calcium salt of malic acid are readily soluble in water, while the normal calcium salt is only sparingly soluble.

The constitution follows from its methods of preparation from the fact that it is readily reduced to succinic acid, and that its esters react with acetic anhydride, yielding mono-acetyl derivatives.

**Amides and Amines of Malic Acid.**—Like glycollic acid, malic acid forms—as an acid—amides (saponifiable), and—as an alcohol—an amine (not saponifiable). The amides are:

**Malamide**,  $\text{NH}_2\cdot\text{CO}\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}_2$ , crystallizing in prisms, and **malamic acid**,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CO}\cdot\text{NH}_2$ , the latter being only known as ethyl ester. The amino-acid, **aspartic acid**,  $\text{CO}_2\text{H}\cdot\text{CH}(\text{NH}_2)\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , unites in itself, like glycocoll, the properties of a base and of an acid, but the acid character predominates. Its acid amide, **asparagine**,  $\text{CO}_2\text{H}\cdot\text{CH}(\text{NH}_2)\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}_2$ , which is isomeric with malamide, is very widely distributed in the vegetable kingdom, being present in the young leaves of trees, in beet-root, potatoes, the shoots of peas, beans, and vetches, and in asparagus; it was first found in the last-named vegetable in the year 1805. It forms glistening rhombic prisms ( $+\text{H}_2\text{O}$ ), is readily soluble in hot water, but insoluble in alcohol and ether, and yields aspartic acid when hydrolysed. It is lævo-rotatory.

A dextro-rotatory asparagine has likewise been obtained from the shoots of vetches; it possesses a sweet taste, and unites with the lævo-rotatory compound to an inactive modification.

**Aspartic acid**, *amino-succinic acid*, is present in beet molasses, and forms an important product of the decomposition of proteins with acids or alkalis. It has been synthesized, e.g. from bromo-succinic acid and ammonia, and crystallizes in small rhombic plates readily soluble in hot water. It exists in optically active modifications, which differ in taste and are convertible the one into the other. Nitrous acid transforms both aspartic acid and asparagine into malic acid.

**Glutamic acid**,  *$\alpha$ -amino-glutaric acid*,  $\text{CO}_2\text{H}\cdot\text{CH}(\text{NH}_2)\cdot\text{CH}_2\cdot$

$\text{CH}_2\text{-CO}_2\text{H}$ , and glutamine correspond with aspartic acid and asparagine. The former is found in beet-root and in the shoots of the vetch and gourd, while the latter is produced, together with aspartic acid and leucine, by boiling proteins with dilute sulphuric acid.

## D. Dihydroxy Dibasic Acids

These acids are characterized by the presence of two hydroxyl radicals in the molecule in addition to two carboxyls.

**Tartaric acid**, *Butane-diol diacid*, *dihydroxy-succinic acid*,  $\text{CO}_2\text{H}\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot(\text{CO}_2\text{H})$ , exists in four distinct modifications.

1. *d*- or **Dextro-tartaric acid**, m.-pt.  $170^\circ$ .
2. *l*- or **Lævo-tartaric acid**, *anti-tartaric acid*, m.-pt.  $170^\circ$ .
3. **Racemic acid**, *d-l-tartaric acid*, *para-tartaric acid*, m.-pt.  $206^\circ$ .
4. *i*- or **Inactive tartaric acid**, *meso-tartaric acid*, m.-pt.  $143^\circ$ .

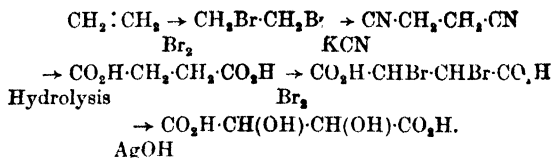
The constitution of these acids follows from their relationship to succinic acid, from their methods of formation, and from the fact that their esters with acetic anhydride yield *diacetyl* derivatives.

Solutions of equal concentration of the two first of these acids turn the plane of polarization of light in an equal degree, but in opposite directions. By their union the inactive racemic acid is formed, and this can, conversely, be separated into its components. The fourth tartaric acid, also inactive, cannot be resolved in this way.

The common tartaric acid found in nature is optically active, and is the *d*-tartaric acid, whereas the acids obtained synthetically are optically inactive, viz. racemic acid or meso-tartaric acid, or a mixture of both, e.g. dibromo-succinic acid with moist silver oxide yields a mixture of racemic and meso-tartaric acids.

Fumaric acid when oxidized with permanganate is converted into racemic acid, and maleic acid by a similar process into meso-tartaric acid (p. 282). Glyoxal cyanhydrin (p. 253) when hydrolysed yields racemic acid, and finally, mannitol when oxidized with nitric acid yields racemic acid, and sorbitol meso-tartaric acid.



*Synthesis:*

**Stereo-isomerism of the Tartaric Acids.**—The isomerism of the tartaric acids is of much the same type as that discussed in the case of active valeric and of  $\alpha$ -lactic acid. A glance at the constitutional formulæ for the acids shows the presence of 2 asymmetric carbon atoms; to each of these 2 atoms are attached the radicals H, OH, and  $\text{CO}_2\text{H}$ , and the remaining valency of each carbon is employed in attaching it to the other carbon atom.

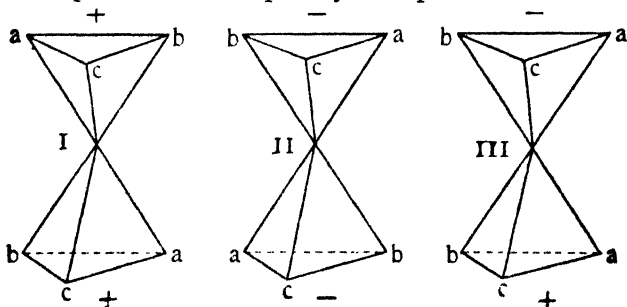
A compound of this general type,  $\text{C}(\text{a}, \text{b}, \text{c}) \cdot \text{C}(\text{a}, \text{b}, \text{c})$ , is known as a compound containing 2 similar asymmetric carbon atoms. If one valency of each carbon is employed in uniting the 2 carbon atoms together, then the 3 radicals, a, b, c, which are attached to the remaining three valencies of a carbon atom, may be arranged in two distinct ways, viz.  $\overset{\text{a}}{\curvearrowright} \overset{\text{b}}{\text{c}}$ , positive order, and  $\overset{\text{a}}{\curvearrowleft} \overset{\text{b}}{\text{c}}$ , negative order.

The following combinations are thus possible:

+	—	+	—
+	—	—	+
or I	2	3	4

But Nos. 3 and 4 must be identical, as the radicals attached to the 2 asymmetric carbon atoms are identical.

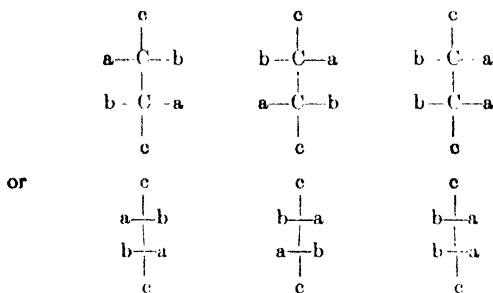
These spatial relationships may be represented:



where  $\text{a} = \text{H}$ ,  $\text{b} = \text{OH}$ , and  $\text{c} = \text{CO}_2\text{H}$ .

*Note.*—At first sight it appears as though the radicals a, b, c in the lower half of fig. 1 were arranged in the — and not the + order, as indicated. It must be remembered, however, that each part of the molecule must be looked at from the same point of view; and if we take the order of the radicals in the upper tetrahedron when arranged so that the solid angle which represents the point of attachment to the second tetrahedron is pointed down, then we must regard the second tetrahedron from the same point of view, i.e. we must turn the figure upside down. It is then seen that the arrangement in the lower half of the molecule is the +.

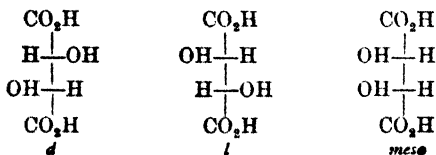
For simplicity the above figures are usually depicted by their projections on a plane surface (*E. Fischer*, B., 1891, 2684):



*Note.*—The manner in which these projection formulæ are obtained can be best seen by means of models.

A comparison of the three configurations at once shows that Nos. I and II are enantiomorphous, and are related to one another as object to mirror image; they should therefore represent the two optically active tartaric acids, and the compound of the two should represent the molecule of racemic acid. No. III has a plane of symmetry, and should therefore represent the non-resolvable, inactive acid—meso-tartaric acid.

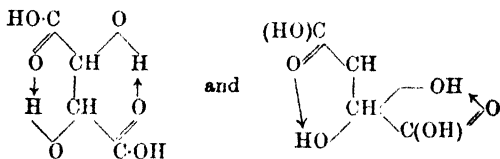
The question as to whether No. I represents *d*- or *l*-tartaric acid has been settled by *Fischer* (B., 1896, 1377) in favour of the *d*-acid. We thus have:



1. **Dextro-tartaric acid**, *acidum tartaricum*, is the tartaric acid found in nature. It was discovered by *Scheele* in 1769. It occurs in the free state, but chiefly as acid potassium salt, in various fruits, especially in the juice of grapes, from which potassium hydrogen tartrate (argol or crude cremor tartari) separates in crystals during fermentation. When this is boiled with chalk and chloride of calcium it is transformed into the neutral calcium salt, from which the acid is liberated on addition of  $\text{H}_2\text{SO}_4$ .

It crystallizes from water in large transparent monoclinic prisms, of a strong taste, is readily soluble in water, also in alcohol, but almost insoluble in ether. It melts at  $170^\circ$ , and its aqueous solution reduces a warm ammoniacal silver solution. When melted, it changes into an amorphous modification, and then into an anhydride, and when heated more strongly it chars, producing a characteristic odour and yielding pyro-racemic and pyro-tartaric acids. Oxidation converts it either into dihydroxy-tartaric (this Chap., F.) or tartronic acid, and then into carbonic acid. It is employed in medicine and dyeing, and for making effervescent drinks.

The abnormal rotations observed in solutions of the acid with concentration and change of wave-length of light may be due to the play of co-ordinate links, e.g.:



**Normal potassium tartrate**,  $\text{C}_4\text{H}_4\text{O}_6\text{K}_2 + \frac{1}{2}\text{H}_2\text{O}$ , forms monoclinic prisms easily soluble in water. **Acid potassium tartrate**, **tartar**, or **cremor tartari**,  $\text{C}_4\text{H}_5\text{O}_6\text{K}$ , small rhombic crystals of acid taste, sparingly soluble in water, is much used in dyeing, medicine, &c. **Potassium sodium tartrate**, **Rochelle** or **seignette salt**,  $\text{C}_4\text{H}_4\text{O}_6\text{KNa} + 4\text{H}_2\text{O}$  (1672), forms magnificent rhombic prisms. **Calcium tartrate**,  $\text{C}_4\text{H}_4\text{O}_6\text{Ca} + 4\text{H}_2\text{O}$ , is a powder insoluble in water, but soluble in cold caustic-soda solution; on warming the solution it separates as a jelly, which redissolves upon cooling. **Potassium antimonyl-tartrate**, **tartar emetic**,  $\text{C}_4\text{H}_4\text{O}_6(\text{SbO})'\text{K} + \frac{1}{2}\text{H}_2\text{O}$ , is obtained by heating cremor tartari with antimony oxide and water. It crystallizes

in rhombic efflorescent octahedra, readily soluble in water. It is poisonous and acts as an emetic, and is used as a mordant in dyeing.

*Fehling's solution* is a solution of cupric sulphate mixed with alkali and Rochelle salt, and is largely used as an oxidizing agent. Thus with various carbon compounds, such as formaldehyde, glucose, fructose, &c., it readily yields a precipitate of cuprous oxide. The copper is present attached to the O atoms

of the two OH groups and present as the ion  $\bar{\text{CO}}_2\cdot\text{CH}\cdot\text{CH}\cdot\bar{\text{CO}}_2$

$$\begin{array}{c} | \quad | \\ \text{O}\cdot\text{Cu}\cdot\text{O} \end{array}$$

The **diethyl ester** is a thick oil, while the **monoethyl ester** crystallizes in prisms. **Aceto-tartaric acid** and **amides** of tartaric acid are known, and also various anhydrides. As an alcohol, it forms with nitric acid a dinitric ester, the so-called **nitro-tartaric acid**,  $\text{C}_2\text{H}_2(\text{O}\cdot\text{NO}_2)_2(\text{CO}_2\text{H})_2$ , which is readily hydrolysed, yielding dihydroxy-tartaric or tartronic acid.

2. **Lævo-tartaric acid** is identical in its chemical and also in almost all its physical properties with ordinary tartaric acid, but differs from it in that its solutions turn the plane of polarization of light to the left, in a degree equal to that in which the other turns it to the right. The crystallized salts show hemihedral faces like the salts of dextro-tartaric acid, but oppositely situated (see p. 290). When equal quantities of both acids are mixed together in aqueous solution, the solution becomes warm, yielding:

3. **Racemic acid**,  $(\text{C}_4\text{H}_6\text{O}_6)_2, 2\text{H}_2\text{O}$ , the composition of which was first established by *Berzelius*, who recognized it as being different from tartaric acid, and who developed the idea of isomerism from this first example in 1829. Racemic acid is obtained from tartar mother liquor. It differs from dextro-tartaric acid in that its crystals are rhombic and efflorescent, and also less soluble in water than the former; further, the free acid is capable of precipitating a solution of calcium chloride and is optically inactive (see below). The salts, which are termed **racemates**, and also the esters, show small differences from the **tartrates** in the proportions of their water of crystallization, in solubility, and melting-point or boiling-point. Molecular-weight determinations of dilute aqueous solutions of racemic acid indicate that under these conditions it is completely resolved into *d*- and *l*-tartaric acids.

4. **Meso-tartaric acid**, a fourth tartaric acid, is inactive like the foregoing, but non-resolvable into the active acids. When heated with water at  $170^{\circ}$  it is partially transformed into racemic acid, which can then be resolved. It differs from racemic acid and also from the active acids in all its physical properties. It crystallizes in efflorescent rectangular plates, m.-pt.  $143^{\circ}$ . The acid-potassium salt is readily soluble in water. For historical sketch of tartrates cf. *Lowry*, Optical rotatory power, 1935.

**Racemic Compounds.** *Resolution of Racemic Compounds into their Optically Active Components.*—Racemic acid has been resolved by three distinct methods, all due to *Pasteur*; and similar methods can be used for the resolution of other racemic compounds (cf. also Chap. L, A).

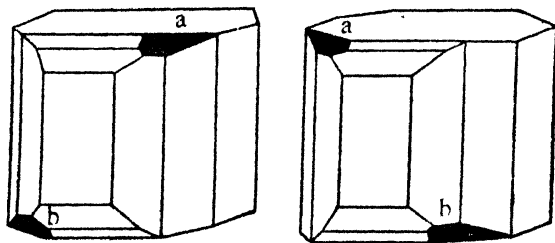
1. When a solution of sodium-ammonium racemate, '



is evaporated, beautiful rhombic crystals having the composition  $\text{NaNH}_4\text{C}_4\text{H}_4\text{O}_6, 4\text{H}_2\text{O}$  and showing hemihedral faces\* are obtained. *Pasteur* observed that these faces were not always similarly situated, but that certain crystals were dextro-hemihedral, while others were lævo-hemihedral, so that one crystal formed the reflected image of the other. The lævo-hemihedral crystals when dissolved exhibit dextro-rotation and vice versa. If now the two kinds of crystals be

\* *Hemihedral Faces.*—These are small faces which are not perfectly symmetrically situated with respect to the other crystalline faces; they occur in only half the positions where they might be expected, and thus give the crystals a non-symmetric structure.

The following figs. represent crystals of the *d*- and *l*-sodium ammonium tartrates:

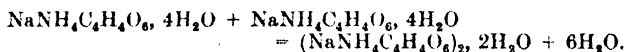


The faces *a* and *b* are the hemihedral faces, and it will be noticed that the two crystals are non-superposable, but stand in the relationship of object to mirror-image.

separated mechanically, and the free acid liberated from each, this will be found to consist, not of racemic acid, but in the one case of *d*- and in the other of *l*-tartaric acid.

In the process of crystallization it is essential that the temperature should be below 27°, as otherwise in place of the enantiomorphously related crystals of sodium-ammonium *d*- and *l*-tartrates, it is found that the crystals are all alike, possess no hemihedral faces, and consist of sodium-ammonium racemate. This temperature is termed the transition point, and for each racemic compound there is a definite transition temperature. Thus for sodium-potassium racemate it is 3°, for rubidium racemate 40.4°, for ammonium-hydrogen malate 74°.

The transition temperature may be determined by means of a dilatometer. This is a large thermometer, the bulb of which is filled with an equimolecular mixture of the two active salts covered with oil, the level of which can be read off on the stem. As the temperature of the dilatometer is raised gradually, a considerable increase in volume is noticed at 27°, due to the change:



Other racemic compounds have been resolved by this simple method of crystallization. In all cases the temperature employed must be below the transition temperature of the given substance, i.e. below the temperature at which the mixture of active components becomes transformed into the racemic compound. In this method of resolution no differences in solubility of the two components are met with, and hence no process of fractional crystallization can be employed; the two salts are deposited side by side, and must be picked out individually. The resolution of zinc ammonium lactate has already been mentioned (p. 247); further examples are sodium-potassium racemate, asparagin, and camphoric acid.

If crystallization occurs in the presence of an optically active solvent, e.g. solution of *l*-malic acid, then a partial separation of antipodes may occur; cf. *McKenzie and Walker* (J. C. S., 1922, 349).

2. A very common method of resolving racemic acids is by combination with an optically active base, e.g. an alkaloid. In the case of racemic acid itself, *Pasteur* used *l*-cinchonine. The two salts formed are (a) *d*-acid + *l*-base, (b) *l*-acid + *l*-base.

As these two salts are not enantiomorphously related, i.e. their molecules do not stand in the relationship of object to mirror-image, they possess different solubilities, and may be separated by fractional crystallization.

The following is a list of some simple racemic compounds which have been resolved by this method; the salt named is the less soluble of the two, and crystallizes first.

Acids.—Quinine: *d*-tartrate. Strychnine: *l*-lactate, *d*-methyl-succinate, *d*-methoxy-succinate, *d*-phenyldibromopropionate. Cinchonine: *l*-tartrate, *d*-malate, *d*-mandelate. Brucine: *d*-tartrate, *l*-valerate, *l*-aspartate.

Racemic bases may be resolved by a similar process, viz. by combination with an optically active acid, e.g. *d*-tartaric, or even better, *d*-bromocamphor-sulphonic acid, and separating the two salts thus obtained by fractional crystallization. Thus ethyl-piperidine and coniine have been resolved by *Ladenburg* by using *d*-tartaric acid (A., 1888, 247, 85; cf. also *Pope* and *Harvey* on resolution of tetrahydro- $\beta$ -naphthylamine, J. C. S., 1901, 74; also *Pope* and *Peachey*, *ibid.* 1899, 1066 and 1105).

3. The third method consists in subjecting a solution of an ammonium salt of the acid to the action of some of the lower plant organisms, e.g. moulds, bacteria, yeasts, &c. Different organisms are required in different cases. *Pasteur* found that ordinary green mould—*Penicillium glaucum*—when grown in a solution of ammonium racemate, destroys the salt of the *d*-acid and leaves a solution of the salt of the *l*-acid. If, however, the decomposition is allowed to proceed, the *l*-salt is also destroyed; the reaction is a preferential decomposition, and, if stopped at a suitable time, practically all *d*-salt will have disappeared. It is obvious that in this method one of the active components is lost; but by using two distinct organisms in separate solutions it is sometimes possible to obtain both *d*- and *l*-compounds. Thus *Penicillium glaucum* grown in a solution of a salt of *d*-*l*-mandelic acid leaves the *d*-salt, and *Saccharomyces ellipsoideus* leaves the *l*-salt.

Among other resolutions which have been effected by this method may be mentioned the destruction of *l*-lactic, *l*-mandelic, *d*-glyceric, *l*-ethoxy-succinic acids, and of *d*-methylpropyl-carbinol by *Penicillium glaucum*, and the destruction of *d*-mandelic, *l*-phenyldibromo-propionic acids and of *d*-glucose, *d*-fructose, and *d*-mannose by yeast (different species).

4. *Markwald* and *M'Kenzie* (B., 1901, 469) have used the method of esterifying the racemic acid with an optically active alcohol. They used *r*-mandelic acid and *l*-menthol, and found that the *d*-component of the racemic acid was esterified somewhat more rapidly than the *l* (cf. also *Mackenzie*, J. C. S., 1904, 378).

*Wren* and *Wright* (J. C. S., 1921, 798) find that the mixture of esters derived from *dl*- $\alpha$ -hydroxy- $\beta$ -phenylpropionic acid and *l*-menthol when crystallized from light petroleum yields the *l*-menthyl ester of the *d*-acid in well-defined crystals, and on hydrolysis this gives the *d*-acid.

5. *Ostromisslensky* (B., 1908, 3035) has shown that a mixture of *d*- and *l*-isomerides can be easily separated if a supersaturated solution of the mixture is impregnated with a crystal of a suitable active material, thus a crystal of *l*-asparagine (p. 284) immediately produces the deposition of *d*-sodium ammonium tartrate from a supersaturated solution containing the *d*- and *l*-salts. It is not necessary that the impregnating substance should be optically active; it must, however, be isomorphous or isodimorphous. Thus a crystal of glycine can cause the deposition of *l*-asparagine from a supersaturated solution of *d*-*l*-asparagine. This method of resolution cannot be used when the supersaturated solution contains a definite racemic compound of the *d*-*l*-isomerides, and can thus be used as a method for determining whether the given substance exists in solution as a *d*-*l* conglomerate or as a true racemic compound.

*M'Kenzie* and *Walker* (J. C. S., 1922, 349) find that certain racemates crystallized from aqueous solutions of *l*-malic acid yield a mixture of the racemate and *d*-tartrate.

*Racemization*.—When *d*-tartaric acid is heated with a small amount of water at 175° racemic acid and a little meso acid are formed. This conversion of a *d*- or *l*-compound into its racemic isomeride is termed *racemization*, and is due to the transformation of 50 per cent of the original active acid into its optical isomer. Other examples of racemization are (a) the heating of *d*-valeric acid with concentrated sulphuric acid, (b) of amyl alcohol with sodium hydroxide. (c) Valeric acid boiled for eighty hours is partially racemized, as is indicated by a slight diminution in its rotatory power. Racemization often occurs during a chemical reaction; thus *l*-mandelic acid,  $C_6H_5\cdot CH(OH)\cdot CO_2H$ , and hydrobromic acid at 50° yield not *l*-phenylbromo-acetic but *r*-phenylbromo-acetic acid. (Cf.



also *Easterfield*, J. C. S., 1891, 72; *Pope*, *ibid.* 1901, 81; *James and Jones*, *ibid.* 1912, 1158.

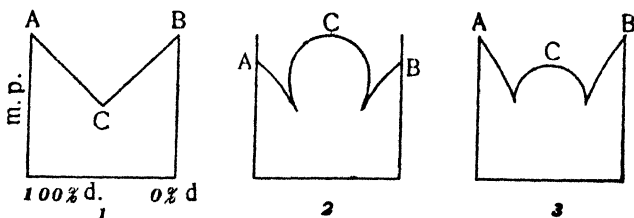
Occasionally the racemization occurs at the ordinary temperature, and is then termed *autoracemization*; thus *d*-phenyl-bromo-acetic acid when kept in benzene solution for some three years becomes quite inactive, and ethyl *d*-bromo-succinate in the course of four years diminishes in rotatory power from  $+40.96^\circ$  to  $+9^\circ$  (*Walden*, B., 1898, 1416).

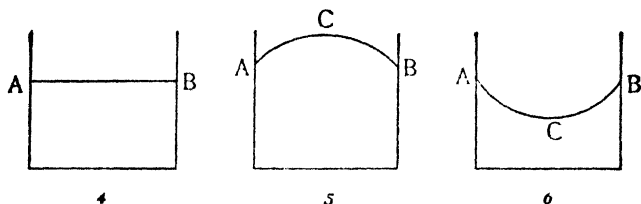
*Criteria for Determining the Nature of the Racemic Compound.*—The racemic substance may be one of the following: (a) A definite compound of 1 molecule of the *d*-component with 1 of the *l*. (b) An ordinary mixture of the two in molecular proportions. (c) Mixed crystals, i.e. a solid solution of the two isomorphous antipodes without chemical combination. The first are termed racemic compounds proper, the second inactive conglomerates, and the third pseudoracemic compounds (*Kipping and Pope*, J. C. S., 1897, 989).

A true racemic compound cannot be recognized by molecular-weight determinations, as in the gaseous form or in solution it is usually resolved into its components. In certain cases the recognition of the substance as a racemic compound is simple, e.g. sodium-ammonium racemate, which crystallizes in a different crystallographic system, and contains a different amount of water of crystallization from the active isomers, and possesses a definite transition point.

When such simple criteria are of no use, *Backhuis Roozeboom* (*Zeit. Phys.*, 1899, **28**, 494) recommends a study of the melting-point curves. These are obtained by taking the melting-points of mixtures of the compounds in different proportions, and then plotting the melting-points against the composition. The following types of curves are met with:

Conglomerates, fig. 1. Racemic compounds, figs. 2 and 3. Mixed crystals, figs. 4, 5, and 6.





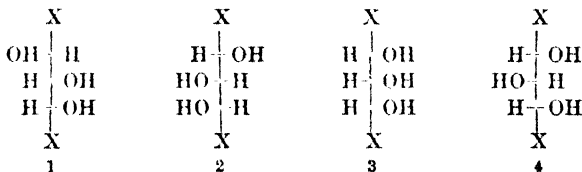
A represents the melting-point of the pure *d*-compound, B that of the pure *l*, and C that of the racemic compound or mixture. These curves should be studied by aid of the Phase rule.

### E. Polyhydroxy Dibasic Acids

Trihydroxy - glutaric acid,  $\text{CO}_2\text{H} \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2\text{H}$ , and the stereo-isomeric acids—saccharic, mucic, and isosaccharic acid —  $\text{CO}_2\text{H} \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2\text{H}$ , are the best-known examples.

Many of these acids form lactones (p. 249), the lactonic acids, and some of them also double lactones.

**Trihydroxy-glutaric acid**,  $\text{CO}_2\text{H} \cdot (\text{CH} \cdot \text{OH})_3 \cdot \text{CO}_2\text{H}$ , is a frequent oxidation-product of sugar varieties, e.g. of xylose and arabinose. According to theory, four stereo-isomers should exist, and four are actually known; they may be represented by the following projection formulæ, where  $\text{X} = \text{CO}_2\text{H}$ :



Nos. 1 and 2 are enantiomorphously related and optically active, and can form a racemic compound. Compounds 3 and 4 are inactive substances of the type of mesotartaric acid.

**Saccharic acid**,  $\text{CO}_2\text{H} \cdot (\text{CH} \cdot \text{OH})_4 \cdot \text{CO}_2\text{H}$ , is produced by the oxidation of cane-sugar glucose, gulose, gulonic acid, mannitol, or starch by nitric acid, and exists in the *d*-, *l*-, and *r*-forms (see Glucoses); *d*-saccharic acid when reduced yields the aldehydo trihydroxy acid, glycuronic acid (see p. 255).

The stereo-isomeric **Mucic acid** is formed by oxidizing dulcitol, the gums, mucilages, and milk-sugar. It is a sparingly soluble, colourless, crystalline powder. The molecule being symmetrical in structure, it is optically inactive. It is easily converted into derivatives of furane (Chap. XL).

**Isosaccharic acid** is obtained by the oxidation of glucosamine,  $C_6H_{11}O_5(NH_2)$ .

Theoretically, ten stereo-isomeric acids of the formula  $CO_2H \cdot [CH \cdot OH]_4 \cdot CO_2H$  are possible, most of which (e.g. **d**- and **i**-manno-saccharic acids, **talomucic acid**, &c.) have been prepared by *E. Fischer*. For their relations to the hexoses see the table appended to these (Chap. XIV, A.).

## F. Dibasic Ketonic Acids

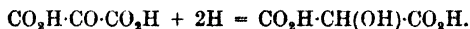
Dibasic ketonic acids unite in themselves the properties of a ketone and of a dibasic acid. The following are known:

1. **Mesoxalic acid**,  $CO(CO_2H)_2$  or  $C(OH)_2(CO_2H)_2$  (see p. 230), is prepared from dibromo-malonic acid,  $CBr_2(CO_2H)_2$ , and baryta water or oxide of silver:



also by boiling alloxan (Chap. XIII, C.) with baryta water. It crystallizes in deliquescent prisms (+ $H_2O$ ).

As a ketone it combines with  $NaHSO_3$ , reacts with hydroxylamine, and is reduced by nascent hydrogen to tartronic acid:



Since the acid and its salts still retain a molecule of water at temperatures above  $100^\circ$ , this may be united in much the same manner as the water in chloral hydrate, corresponding with the formula  $C(OH)_2(CO_2H)_2$ , "dihydroxy-malonic acid". In fact, two modifications of the ethyl ester are known, viz.  $C(OH)_2(CO_2C_2H_5)_2$  and  $CO(CO_2C_2H_5)_2$ .

2. **Oxal-acetic acid**, *Butanone diacid*,  $CO_2H \cdot CH_2 \cdot CO \cdot CO_2H$ , is an acid corresponding in many respects with aceto-acetic acid. Its **ethyl ester** is prepared by the action of sodium ethoxide upon a mixture of ethyl oxalate and acetate (p. 258), and also by the action of concentrated sulphuric acid upon ethyl acetylene-dicarboxylate. It is a colourless oil, but the alco-

holic solution gives an intense dark-red coloration with ferric chloride. It is of importance as a synthetical reagent, as the hydrogen atoms of the methylene group can be replaced by sodium, and hence by various alkyl and acyl radicals.

3. **Acetone-dicarboxylic acid**, *Pentanone diacid*,  $\text{CO}(\text{CH}_2\cdot\text{CO}_2\text{H})_2$ , obtained by treating citric acid with concentrated  $\text{H}_2\text{SO}_4$ , readily decomposes into acetone and  $2\text{CO}_2$ .

4. **Dihydroxy-tartaric acid**,  $\text{CO}_2\text{H}\cdot\text{CO}\cdot\text{CO}\cdot\text{CO}_2\text{H}$ , or probably  $\text{CO}_2\text{H}\cdot\text{C}(\text{OH})_2\cdot\text{C}(\text{OH})_2\cdot\text{CO}_2\text{H}$ , is formed from pyrocatechol and nitrous acid, and by the gradual decomposition of nitro-tartaric acid. It melts at  $98^\circ$ . The characteristic sparingly soluble sodium salt decomposes readily into carbon dioxide and sodium tartronate.

5. **Diaceto-succinic acid**,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}\cdot\text{CO}_2\text{H}$   
 $\text{CH}_3\cdot\text{CO}\cdot\dot{\text{C}}\text{H}\cdot\text{CO}_2\text{H}$  (see p. 263).

The ester of this is closely related to acetonyl-acetone, the latter being readily obtainable from the former by the action of caustic-soda solution ("Ketonic decomposition"; cf. B., 1900, 1219).

6. **Diacetoglutaric acid**,  $\text{CO}_2\text{H}\cdot\text{CHAc}\cdot\text{CH}_2\cdot\text{CHAc}\cdot\text{CO}_2\text{H}$ . The ester of this acid is formed by condensing ethyl acetoacetate with formaldehyde in the presence of diethylamine, and is readily converted into derivatives of tetrahydrobenzene or pyridine (*Knoevenagel*, A., **281**, 94; cf. also B., 1899, 1388).

Most of these ketonic acids exhibit keto-enolic tautomerism, thus 5 isomerides of diacetyl-succinic acid are known (*Knorr*, A., 1899, **306**, 332; cf. Chap. LIII, A.).

## XI. POLYBASIC ACIDS

The polybasic acids contain three or more carboxylic groups in the molecule. The tribasic acids, like phosphoric acid, can give rise to three series of salts—normal, monoacid, and diacid. Both saturated and unsaturated acids are known, and also substituted derivatives.

### A. Saturated and Unsaturated Polybasic Acids

A simple tribasic acid is **tricarballic acid**, *symmetrical propane-tricarboxylic acid*,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}(\text{CO}_2\text{H})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ . It occurs in unripe beet, and is prepared (a) by the addition of hydrogen to aconitic acid, (b) by heating citric acid with hydriodic acid, and (c) synthetically from glycerol by transforming it into the tribromhydrin,  $\text{C}_3\text{H}_5\text{Br}_3$ , treating this with KCN, and hydrolysing the cyanide formed,  $\text{C}_3\text{H}_5(\text{CN})_3$ . Its structure as  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}(\text{CO}_2\text{H})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  follows from its formation from glycerol.

This acid is of importance in determining the constitution of citric acid, from which, as already seen, it can be obtained by reduction with HI. It crystallizes in rhombic prisms, is readily soluble in water, and melts at  $166^\circ$ .

An unsaturated tribasic acid closely related to tricarballic acid is **aconitic acid**,  $\text{CO}_2\text{H}\cdot\text{CH}:\text{C}(\text{CO}_2\text{H})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , which contains two atoms of hydrogen less than tricarballic acid. It is found in nature, in *Aconitum Napellus*, shave-grass, sugarcane, beet-root, &c., and is prepared by heating citric acid,  $\text{C}_6\text{H}_8\text{O}_7$ , when the elements of water are eliminated. It is a strong acid, crystallizable, readily soluble in water, melts at  $191^\circ$ , and is reduced by nascent hydrogen to tricarballic acid, hence its constitution.

### B. Hydroxy Polybasic Acids

**Citric acid**, *acidum citricum*, *hydroxy-tricarballic acid*,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{C}(\text{OH})(\text{CO}_2\text{H})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  (Scheele, 1784; recognized as tribasic by Liebig in 1838), occurs in the free state in lemons, oranges, and red bilberries, and mixed with malic acid in gooseberries, &c., also as calcium salt in woad, potatoes, beet-root, &c. It can be manufactured from the juice of lemons by precipitating as its calcium salt, but the more common method is by the action of mould fungi, especially *Citromyces citrinus* on glucose solutions kept at a  $\text{p}_\text{H} = 3.5$  by the addition of  $\text{CaCO}_3$  and a temperature of  $20^\circ\text{--}30^\circ$  for 9–10 days. It crystallizes in large rhombic prisms ( $+\text{H}_2\text{O}$ ), is readily soluble in water, moderately in alcohol, but only sparingly in ether. It loses its water of crystallization at  $130^\circ$ , melts at  $153^\circ$ , and

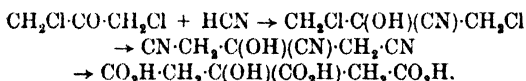
breaks up at a higher temperature first into aconitic acid and water, and then into carbon dioxide, itaconic acid, citraconic anhydride, and acetone. Oxidizing agents effect a very thorough decomposition.

Mono-, di-, and tri-alkali salts are all soluble, whereas the calcium salt is insoluble. Among the derivatives may be mentioned **mono-, di-, and triethyl citrates** and **triethyl aceto-citrate**,

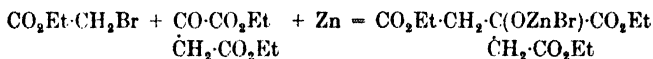


The formation of this last is a direct proof of the alcoholic character of citric acid. The **amides** of citric acid are converted by concentrated  $\text{H}_2\text{SO}_4$  into **citrazinic acid**,  $\text{C}_6\text{H}_5\text{NO}_4$ , a pyridine derivative.

The *constitution* of citric acid is arrived at (a) from its conversion into aconitic acid by the elimination of water, (b) from its reduction to tricarballic acid, and (c) from its synthesis from 1 : 3 dichloroacetone, e.g.:



The acid has been synthesized by *Lawrence* (J. C. S., 1897, 457) by an application of *Reformatsky's* reaction, i.e. the condensation of a halogen derivative with a ketone in the presence of zinc (cf. p. 142), viz. ethyl bromacetate, ethyl oxalacetate, and pure zinc turnings:



This condensation product reacts with water, yielding ethyl citrate,  $\text{CO}_2\text{Et}\cdot\text{CH}_2\cdot\text{C}(\text{OH})(\text{CO}_2\text{Et})\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ , zinc oxide, and hydrogen bromide.

Acids containing more than three carboxylic groups do not, as a rule, occur in nature, but a number of esters of such acids have been prepared by means of the aceto-acetic ester, malonic ester and cyanoacetic ester syntheses.

## XII. CYANOGEN COMPOUNDS

Under the name of the cyanogen compounds is included a group of substances which are derivable from cyanogen,  $C_2N_2$ . Cyanogen itself is a gas of excessively poisonous properties which behaves in many respects like a halogen; and its hydrogen compound, hydrocyanic acid, HCN, is an acid resembling hydrochloric acid to a certain extent. In many cyanogen compounds the monovalent group (CN) plays the part of an element; cyanogen is to be regarded as the isolated radical (CN), which, however, possesses the double formula  $C_2N_2$ , just as a molecule of chlorine ( $Cl_2$ ) is made up of two atoms. The cyanogen group is further capable of combining with the halogens, hydroxyl, sulphhydryl (SH), amidogen, &c. From the compounds so obtained numerous others are derived by the entrance of alkyl radicals in place of hydrogen. Such derivatives invariably exist in two isomeric forms, sharply distinguished from one another by their properties. They are often termed normal and iso compounds, and the isomerism is of very great interest. As polymeric forms are also known, the number of cyanogen compounds is very large.

Carbon and nitrogen do not combine directly except in the presence of an alkali, and then a metallic cyanide is formed. As examples of this reaction, we have the following:

1. When nitrogen is led over a red-hot mixture of coal and carbonate of potash, potassium cyanide, KCN, is formed, especially under a high pressure.

2. Ammonium cyanide is formed when ammonia is passed over red-hot coal.

3. Potassium cyanide is formed when nitrogenous organic compounds such as leather, horn, claws, wool, blood, &c., are heated with potashes.

4. Hydrocyanic acid is formed when electric sparks are passed through a mixture of acetylene and nitrogen, and also by the action of the silent electric discharge on a mixture of cyanogen and hydrogen. It is also formed (commercial method) when a carefully dried mixture of hydrogen, ammonia, and a volatile carbon compound ( $CO$ ,  $CO_2$ ,  $C_2H_2$ , &c.) is passed over heated platinized pumice. (For further modes of formation see p. 302 *et seq.*)

# SUMMARY OF THE CYANOGEN COMPOUNDS

Relation to carbonic acid, &c. (See p. 314)	Name	Formula
Nitrile of oxalic acid,	<i>Cyanogen</i> ,	$\text{N} \vdots \text{C} \cdot \text{C} \vdots \text{N}$
Nitrile of formic acid,	<i>Hydrocyanic acid</i> , Alkyl derivatives: (a) Nitriles, (b) Isonitriles,	$\text{N} \vdots \text{C} \cdot \text{H}$ $\text{R} \cdot \text{C} \vdots \text{N}$ $\text{R} - \text{N} \equiv \text{C}^*$
	<i>Cyanogen chloride</i> , <i>bromide</i> , <i>iodide</i> ,	$\text{N} \vdots \text{C} \cdot \text{Cl}$
$\text{CO}_2\text{H}_2 + \text{NH}_3 - 2\text{H}_2\text{O}$ , (Nitrile of carbonic acid, eventually Carbimide),	<i>Cyanic acid</i> , Alkyl derivatives: (a) Methyl cyanate, (b) „ isocyanate,	$\text{N} \vdots \text{C} \cdot \text{OH}$ $\text{N} \vdots \text{C} \cdot \text{O} \cdot \text{CH}_3$ $\text{O} \vdots \text{C} \cdot \text{N} \cdot \text{CH}_3$
	<i>Thiocyanic acid</i> , Alkyl derivatives: (a) Ethyl thio- cyanate, (b) Allyl isothio- cyanate,	$\text{N} \vdots \text{C} \cdot \text{SH}$ $\text{N} \vdots \text{C} \cdot \text{S} \cdot \text{C}_2\text{H}_5$ $\text{S} \vdots \text{C} \cdot \text{NC}_3\text{H}_5$
$\text{CO}_2\text{H}_2 + 2\text{NH}_3 - 3\text{H}_2\text{O}$ , (Nitrile and amide of car- bonic acid, eventually Carbo-di-imide).	<i>Cyanamide</i> , Alkyl derivatives: (a) Alkyl cyana- mide, (b) Carbo-di-imide,	$\text{N} \vdots \text{C} \cdot \text{NH}_2$ $\text{N} \vdots \text{C} \cdot \text{NH} \cdot \text{R}$ $\text{RN} \vdots \text{C} \cdot \text{NR} \dagger$
The amic acid of car- bonic acid,	<i>Carbamic acid</i> ,	$\text{NH}_2 \cdot \text{CO} \cdot \text{OH}$
The amide of carbonic acid,	<i>Urea</i> ,	$\text{CO}(\text{NH}_2)_2$
	<i>Thio-urea</i> , Alkyl derivatives: (a) Alkyl-thio-ureas, (b) Imido-thio-carba- mine com- pounds,	$\text{CS}(\text{NH}_2)_2$ $\text{NH}_2 \cdot \text{CS} \cdot \text{NHR}$ $\text{NH} \vdots \text{C} \begin{array}{l} \text{NH}_2 \\ \text{SR} \end{array}$
$\text{CO}_2\text{H}_2 + 3\text{NH}_3 - 3\text{H}_2\text{O}$ , (Amidine),	<i>Guanidine</i> ,	$\text{HN} \vdots \text{C}(\text{NH}_2)_2$

\* Electronic formula.

† R = alkyl radical.

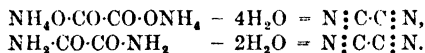


The original material for the preparation of most of the cyanogen compounds is potassium ferrocyanide, which is manufactured on the large scale and possesses the great advantage over potassium cyanide of being stable in the air and comparatively non-poisonous.

### A. Cyanogen and Hydrocyanic Acid

**Cyanogen**,  $\text{N}:\text{C}:\text{C}:\text{N}$ , which was discovered by *Gay-Lussac* in 1815, occurs in the gases of blast-furnaces and in coal gas.

As the nitrile of oxalic acid, it may be obtained by the abstraction of the elements of water from ammonium oxalate or oxamide by means of  $\text{P}_4\text{O}_{10}$ :



It is usually prepared by strongly heating dry silver cyanide,  $\text{AgCN}$ , or mercuric cyanide,  $\text{Hg}(\text{CN})_2$ ,  $\text{Hg}(\text{CN})_2 = \text{Hg} + \text{C}_2\text{N}_2$ ; or by heating a solution of cupric sulphate with potassium cyanide.

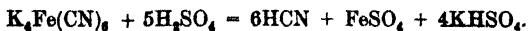
Cyanogen is a colourless, extremely poisonous gas with an odour resembling that of bitter almonds. It is easily liquefied and solidified (sp. gr. 1.8 of the liquid; m.-pt.  $-34^\circ$ ; b.-pt.  $-21^\circ$ ). It dissolves in 0.25 vol. of water and in less alcohol, and the solutions rapidly decompose. Cyanogen combines with heated potassium to  $\text{KCN}$ , and dissolves in aqueous potash to form  $\text{KCN}$  and  $\text{KCNO}$ .

**Paracyanogen**,  $(\text{CN})_x$ , a polymer of cyanogen, is an amorphous brown powder which is formed as a by-product when mercuric cyanide is heated; upon further heating, it is transformed into cyanogen.

**Hydrocyanic acid**, *prussic acid*,  $\text{CNH}$ , was discovered about the year 1782 by *Scheele*, and investigated closely by *Gay-Lussac*.

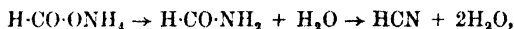
Some of the more interesting methods of formation are the following:

1. It is readily liberated from its salts by the action of almost any other acid, even carbonic acid; and even complex cyanides, e.g. potassium ferrocyanide, when distilled with moderately dilute sulphuric acid yield hydrogen cyanide:

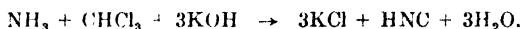


The ferrous sulphate produced reacts with more ferrocyanide to form potassium ferrous ferrocyanide,  $\text{FeK}_2(\text{FeC}_6\text{N}_6)$ , which is not affected by dilute acids (see p. 306); consequently only half of the cyanogen present is converted into hydrocyanic acid. The anhydrous acid is obtained by passing  $\text{H}_2\text{S}$  over lead cyanide and condensing the product in a freezing mixture. When concentrated sulphuric acid is employed, carbon monoxide is obtained from the intermediate product, formic acid, but by adding the acid drop by drop, anhydrous hydrocyanic acid is formed.

2. As the nitrile of formic acid, it may be prepared by the action of dehydrating agents on ammonium formate or formamide:



and as a carbylamine by warming chloroform and alcoholic potash with ammonia under pressure (cf. p. 113).



3. Together with oil of bitter almonds,  $\text{C}_6\text{H}_5\cdot\text{CHO}$ , and grape-sugar,  $\text{C}_6\text{H}_{12}\text{O}_6$ , by the hydrolysis of the glucoside amygdalin under the influence of the enzyme "emulsin" (see Benzaldehyde, Chap. XXV, B.):



The oil of bitter almonds and its aqueous solution (*aqua amarum amygdalarum*)—prepared from the almonds themselves—consequently contain HCN.

The acid occurs in the free state in the tree *Pangium edule*, found in Java, more particularly in the seeds. It exists in the form of glucosides in various plants termed cyanogenetic plants.

For other syntheses see p. 300.

Hydrogen cyanide is a colourless liquid boiling at  $26^\circ$  and solidifying at  $-14^\circ$ . Sp. gr. 0.70. It has a peculiar odour and produces an unpleasant irritation in the throat, is miscible with water, and burns with a violet flame. Like potassium cyanide, it is one of the most deadly poisons. The best antidotes are stated to be hydrogen peroxide or small quantities of chlorine mixed with air. When absolutely pure it can be preserved unchanged, but it decomposes in presence of traces of water or ammonia, with separation of a brown mass and

formation of ammonia, formic acid, oxalic acid, &c. The addition of minute quantities of mineral acids renders the aqueous solution more stable.

Liquid hydrocyanic acid is a good solvent for many salts, and has a high ionizing power. Acids (sulphuric and trichloroacetic), however, do not appear to dissociate when dissolved in the liquid.

The acid has many properties of an unsaturated compound. It is readily reduced by nascent hydrogen to methylamine. In the presence of hydrochloric acid it combines with water yielding formamide. With diazomethane (Chap. IV, F.) it yields methyl cyanide together with methyl carbylamine. With hydrogen chloride it gives *iminoformyl chloride*,  $\text{NH}:\text{CHCl}$ , a compound of importance in the synthesis of aromatic aldehydes (A., 1906, 347, 347); but has not been isolated. From ethyl acetate solution a product  $2\text{HCN}$ ,  $3\text{HCl} = \text{NH}:\text{CH}\cdot\text{NH}\cdot\text{CHCl}_2$ ,  $\text{HCl}$ , dichloromethyl formamidine hydrochloride is obtained. It combines directly with most aldehydes and ketones, yielding cyanhydrins (nitriles of hydroxy acids) (p. 238), and also with certain unsaturated compounds, especially in the presence of potassium cyanide, yielding saturated nitriles (*Lapworth*, J. C. S., 1903, 995; 1904, 1214; *Knoevenagel*, B., 1904, 37, 4065); e.g.  $\alpha$ -phenylcinnamo-nitrile,  $\text{CHPh}:\text{CPh}\cdot\text{CN}$ , yields diphenylsuccinylo-nitrile,  $\text{CN}\cdot\text{CHPh}\cdot\text{CHPh}\cdot\text{CN}$ .

Hydrocyanic acid is an extremely weak monobasic acid  $K \times 10^{10} = 0.13$ , and its salts are decomposed even by carbonic acid. It is a typical tautomeric compound (cf. Chap. LIII, B.),  $\text{H} - \text{C} \equiv {}^2\text{N} \rightleftharpoons \text{H} - \text{N} \rightleftharpoons {}^2\text{C}$ .

Hydrocyanic acid can be detected by converting it either into Prussian blue or into ferric thiocyanate. In the former case the solution to be tested is treated with excess of caustic soda and some ferrous and ferric salt, boiled, and acidified, when Prussian blue results; in the latter the solution is evaporated to dryness together with a little yellow sulphide of ammonium, the residue taken up with water and ferric chloride added, when the blood-red colour of ferric thiocyanate is obtained.

**Trihydrocyanic acid**,  $(\text{CNH})_x$ , forms white, acute-angled crystals, which readily yield hydrogen cyanide when heated above  $180^\circ$ .

**Cyanides.**—The cyanides of the alkali and alkali-earth

metals are soluble in water, and the solutions have a strongly alkaline reaction due to the hydrolysing action of the water. The salts of the heavy metals, with the exception of mercuric cyanide, are insoluble in water.

**Potassium cyanide**, KCN, forms colourless deliquescent cubes, sparingly soluble in alcohol. The commercial product usually contains large amounts of potassium carbonate due to the action of atmospheric carbon dioxide. It is formed when potassium ferrocyanide is fused, and the product extracted with water:  $K_4FeC_6N_6 = 4KCN + FeC_2 + N_2$ .

*Manufacturing processes.*—(a) *Beilby's process*, which consists in treating a fused mass of potassium carbonate and carbon with ammonia, the product being a molten cyanide of high strength. (b) The sodium salt required for extracting gold from auriferous quartz is made by fusing sodium ferrocyanide, a by-product of gas-works, with sodium  $Na_4FeC_6N_6 + 2Na \rightarrow 6NaCN + Fe$  (*McArthur-Forrest process*).

The pure salt can be prepared by passing hydrogen cyanide into an alcoholic solution of potassium hydroxide. It reacts with hydrogen peroxide in two different ways (cf. *Masson*, J. C. S., 1907, 1449):

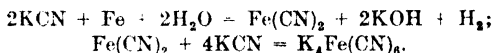
1.  $80\% KCN + H_2O_2 \rightarrow KCNO + H_2O$  and  
 $KCNO + 2H_2O \rightarrow NH_3 + KOH + CO_2$ ;
2.  $20\% KCN + 2H_2O \rightarrow NH_3 + HCOOK$ .

**Mercuric cyanide**,  $Hg(CN)_2$ , crystallizes in colourless prisms, is stable in the air, readily soluble in water, and excessively poisonous. Its aqueous solution is a non-electrolyte. **Silver cyanide**,  $AgCN$ , forms a white flocculent precipitate closely resembling the chloride in appearance, but is soluble in hot concentrated nitric acid.

**Complex Cyanides.**—The double cyanides, which are produced by dissolving the insoluble metallic cyanides in a solution of potassium cyanide, are divided into two classes. The members of the one class are decomposed again on the addition of dilute mineral acids, with separation of the insoluble cyanide and formation of hydrocyanic acid, e.g.  $KAg(CN)_2$ ;  $K_2Ni(CN)_4$ . The gold and silver double salts are largely used in gold and silver electro-plating. The members of the other class are much more stable and do not evolve hydrocyanic acid; to this class belong **potassium ferrocyanide**,  $K_4Fe(CN)_6$ ,  $[Fe(CN)_2, 4KCN]$ , and **Potassium ferricyanide**,  $K_3Fe(CN)_6$ ,  $[Fe(CN)_3,$

3KCN]. The members of this second class are often termed **complex salts**, and are the metallic salts of complex acids, e.g. **hydroferrocyanic acid**,  $\text{H}_4\text{FeC}_6\text{N}_6$ , and **hydroferricyanic acid**,  $\text{H}_3\text{FeC}_6\text{N}_6$ , which are formed when the salts are decomposed with mineral acids, and hence do not give reactions characteristic of the cyanide anion. Certain salts of the latter acid are not decomposed at all by dilute acids, for instance Prussian blue, but they are by caustic potash (which converts Prussian blue into  $\text{Fe}(\text{OH})_3$  and  $\text{K}_4\text{FeC}_6\text{N}_6$ ).

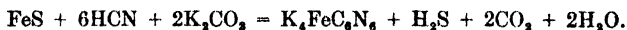
**Potassium ferrocyanide**, *yellow prussiate of potash*,  $\text{K}_4\text{Fe}(\text{CN})_6 + 3\text{H}_2\text{O}$ , may be obtained by adding excess of potassium cyanide to a solution of ferrous sulphate, or by dissolving iron in a solution of cyanide of potassium, when hydrogen is evolved, thus:



The old commercial method consisted in fusing together scrap-iron, nitrogenous organic matter, and crude potassic carbonate.

It is now usually manufactured from the hydrogen cyanide present in crude coal gas or the gas from coke ovens. The spent oxide used in the purification of coal gas contains Prussian blue (ferric ferrocyanide, p. 307). The spent oxide is heated with hot milk of lime, and the Prussian blue thus transformed into calcium ferrocyanide, from which the potassium salt can be prepared.

Another method consists in passing the coal gas, before it has been subjected to dry purification, through an alkaline solution containing an iron salt. The sulphuretted hydrogen reacts with the iron salt, forming ferrous sulphide, and this with the hydrogen cyanide and alkali (potassium carbonate) yields potassium ferrocyanide:



It forms large, lemon-coloured monoclinic plates, which are stable in the air and easily soluble in water, but insoluble in alcohol. Concentrated  $\text{HCl}$  yields **hydro-ferrocyanic acid**,  $\text{H}_4\text{FeC}_6\text{N}_6$ , in the form of white needles. With a solution of  $\text{CuSO}_4$ , a red-brown precipitate of **cupric ferrocyanide**, or *Hatchett's brown*,  $\text{Cu}_2\text{FeC}_6\text{N}_6$ , is thrown down, and with solu-

tions of ferrous and ferric salts the well-known characteristic precipitates (see below). Chlorine oxidizes it to

**Potassium ferricyanide**, *red prussiate of potash*,  $\text{K}_3\text{FeC}_6\text{N}_6$ ,  
 $2\text{K}_4\text{FeC}_6\text{N}_6 + \text{Cl}_2 = 2\text{K}_3\text{FeC}_6\text{N}_6 + 2\text{KCl}$ .

This crystallizes in long, dark-red, monoclinic prisms which are readily soluble in water. The solution decomposes when kept, and acts as a strong oxidizing agent in the presence of alkali, potassium ferrocyanide being reproduced. **Hydroferricyanic acid**,  $\text{H}_3\text{FeC}_6\text{N}_6$ , forms unstable brown needles. In these complex cyanides the CN groups are arranged octahedrally around a central iron atom.

Of industrial importance are the pigments **Prussian Blue**, ferric potassium ferrocyanide,  $\text{KFe}^{\text{III}}[\text{Fe}^{\text{II}}(\text{CN})_6]$ , from a ferric salt and a soluble ferrocyanide or a ferrous salt and a ferrocyanide with aerial oxidation.

**Berlin Blue**, ferric ferricyanide  $\text{Fe}^{\text{III}}[\text{Fe}^{\text{III}}(\text{CN})_6]$ , obtained by oxidation of Prussian blue (cf. *Keggin and Miles, Nature, 1936, 137, 577*).

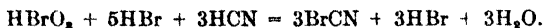
**Insoluble Prussian Blue**, or *Turnbull's Blue*, is a non-electrolyte  $[\text{Fe}_2^{\text{III}}(\text{CN})_6]$ .

**Sodium nitro-prusside**,  $\text{Na}_2\text{FeC}_5\text{N}_5(\text{NO}) + 2\text{H}_2\text{O}$ , crystallizes in red prisms soluble in water, and yields a brilliant but transient violet coloration with alkali sulphides.

## B. Halogen Compounds of Cyanogen

**Cyanogen chloride**,  $\text{Cl:N:C}$  (*Berthollet*), is a colourless gas with an obnoxious odour, and boils at  $15.5^\circ$ . It is prepared by the action of chlorine upon mercuric cyanide or upon dilute aqueous hydrocyanic acid,  $\text{CNH} + \text{Cl}_2 = \text{CNCl} + \text{HCl}$ . It polymerizes readily to cyanuric chloride, and yields sodium chloride and cyanate with aqueous sodium hydroxide.

**Cyanogen bromide**,  $\text{CNBr}$ , forms transparent prisms, and is prepared by the action of sulphuric acid on a mixture of bromate, bromide, and cyanide of sodium:



**Cyanogen iodide**,  $\text{CNI}$ , forms beautiful white prisms, smelling intensely both of cyanogen and iodine, and subliming with the utmost ease (cf. *Chattaway and Wadmore, J. C. S., 1902, 191*).

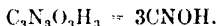
**Cyanuric chloride**, *trichlorocyanogen*,  $(\text{CCl})_3\text{N}_3$ , forms beau-

tiful white crystals with an unpleasant odour, and has m.-pt.  $145^{\circ}$  and b.-pt.  $190^{\circ}$ .

For general discussion of urea, cyanic acid, cyamelide and cyanuric acid, cf. *Chattaway*, J. C. S., 1912, 170; *Werner*, 1913, 1010, 2275.

### C. Cyanic and Cyanuric Acids

Cyanuric acid is formed when urea is heated, either alone or in a stream of chlorine gas; and when this acid is distilled, and the vapour condensed in a freezing-mixture, **cyanic acid**, CNOH, is obtained as a mobile liquid of a pungent odour:



It is exceedingly unstable; when taken out of the freezing-mixture it changes, with explosive ebullition, into a white porcelain-like mass which consists of cyanuric acid 70 per cent, and cyamelide 30 per cent. **Potassium cyanate**, CNOK, is prepared by the oxidation of an aqueous solution of potassium cyanide by means of permanganate; or by fusing potassium cyanide or yellow prussiate of potash with  $\text{PbO}_2$  or  $\text{MnO}_2$ ; ( $\text{CNK} + \text{O} = \text{CNOK}$ ). It crystallizes in white plates, readily soluble in water and alcohol. **Ammonium cyanate**, CNO ( $\text{NH}_4$ ), forms a white crystalline mass, and is of especial interest on account of the readiness with which it changes into the isomeric urea,  $\text{CO}(\text{NH}_2)_2$  (Chap. XIII, C.).

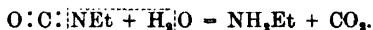
When these salts are decomposed with mineral acids, free cyanic acid is not formed, but its products of hydrolysis, viz. carbon dioxide and ammonia:



This decomposition is avoided by the addition of dilute acetic acid (instead of hydrochloric), but in the latter case the cyanic acid changes into its polymer cyanuric acid, and the hydrogen-potassium salt of the latter slowly crystallizes out.

When the hydrogen atom in the cyanic acid molecule is replaced by alkyl radicals, two distinct groups of compounds are possible. The derivatives which are constituted on the type  $\text{N}:\text{C}\cdot\text{O}\cdot\text{R}$  are termed the *normal*, and those on the type  $\text{O}:\text{C}:\text{N}\cdot\text{R}$  the *iso-compounds*.

**Ethyl isocyanate**, *cyanic ether*,  $\text{O}:\text{C}:\text{N}\cdot\text{CH}_2\cdot\text{CH}_3$ , obtained when potassium cyanate is distilled with ethyl iodide or potassium ethyl-sulphate, is a colourless liquid of suffocating odour, distilling at  $60^\circ$ , and is decomposed by water. It does not behave as a typical ester, since when hydrolysed with acids or alkalis it yields ethylamine and carbon dioxide:



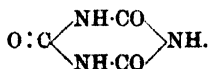
Water, which acts in a similar manner, gives rise to the more complicated urea derivatives; ammonia and amines also produce derivatives of urea, and alcohol yields derivatives of carbamic acid (see Carbonic Acid Derivatives).

The production of ethylamine as one of the products of hydrolysis is usually regarded as a strong argument in favour of the view that in the original isocyanate the ethyl group is attached to nitrogen and not to oxygen, e.g.  $\text{O}:\text{C}:\text{N}\cdot\text{Et}$ . It is questionable, however, whether free cyanic acid and cyanate of potassium possess analogous constitutions, since frequent observations have shown that the normal cyanic compounds readily change into the iso- (see below); theoretical considerations indeed make it more probable that cyanic acid has the constitution  $\text{N}:\text{C}\cdot\text{OH}$ , according to which it appears as the normal acid, with cyanogen chloride as its chloride.

**Normal cyanic esters** are not known (cf. A., 287, 310).

**Cyanuric acid**,  $\text{C}_3\text{N}_3\text{O}_3\text{H}_3$ ,  $= (\text{CN})_3(\text{OH})_3$  (*Scheele*), obtained by heating urea, or by the action of water on cyanuric chloride, forms transparent prisms containing two molecules of water of crystallization. It effloresces in the air, and dissolves readily in hot water. It is a tribasic acid. The sodium salt is sparingly soluble in conc.  $\text{NaOH}$ ; the  $(\text{Cu}\cdot\text{NH}_4)$  salt possesses a characteristic beautiful violet colour. Upon prolonged boiling with hydrochloric acid it is hydrolysed to  $\text{CO}_2$  and  $\text{NH}_3$ , while phosphorus pentachloride converts it into cyanuric chloride.

Only one cyanuric acid is known and, owing to the fact that the N-methyl derivative is obtained by the action of diazo-methane, is represented by the iso-structure:

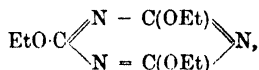


(Compare also *Hantzsch*, B., 1906, 139.)

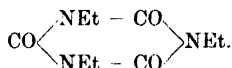


Cyanuric acid is a pseudo acid, as its salts and also chloride have the normal structure. The mercuric salt exists in two isomeric forms.

Two distinct groups of alkyl derivatives are, however, known—**normal cyanuric esters**, e.g. **ethyl cyanurate**,



which is formed by the action of ethyl iodide on silver cyanurate at the ordinary temperature, or by the action of sodium ethoxide on cyanogen chloride or cyanuric chloride, is readily changed into an **isocyanuric ester**, e.g. **ethyl isocyanurate**,



These isocyanurates are often formed instead of the normal compounds if the temperature is not kept low, e.g. when a cyanurate is heated with potassium ethyl-sulphate. They are further formed by the polymerization of the isocyanic esters, being thus obtained as by-products in the preparation of the latter.

The constitution of the normal compounds is largely based on the fact that on hydrolysis they behave as normal esters and yield ethyl alcohol and cyanuric acid. The isocyanurates, on the other hand, usually yield primary amines, e.g. ethylamine, and hence presumably the alkyl group is attached to nitrogen in the isocyanurate molecule.

For mixed normal iso-esters see *Hantzsch and Bauer, B.*, 1905, 1005.

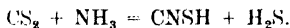
## D. Thiocyanic Acid and its Derivatives

Nearly every oxygen derivative of cyanogen has a sulphur analogue. (*Clayton and Bann, C. and I.*, 1942, 420.)

**Potassium thiocyanate**, *-sulphocyanate*, *-sulphocyanide*, *-rhodanide*, CNSK, is readily formed when potassium cyanide is fused with sulphur, or when an aqueous solution of KCN is evaporated with yellow ammonium sulphide.

It is usually prepared by fusing potassium ferrocyanide with sulphur and potashes. It forms long colourless deliquescent

prisms, extremely soluble in water with absorption of much heat, and also readily soluble in hot alcohol. **Ammonium thiocyanate**,  $\text{CNS}(\text{NH}_4)$ , is formed when a mixture of carbon disulphide, concentrated ammonia, and alcohol (*Millon*) is heated, dithiocarbamate and trithiocarbonate of ammonia being formed as intermediate products:



It forms colourless deliquescent plates, readily soluble in alcohol, and when heated to  $130^\circ$ – $140^\circ$  is partially transformed into the isomeric thio-urea, just as ammonium cyanate is into urea. It precipitates **silver thiocyanate**,  $\text{CNSAg}$ (white), from solutions of silver salts, and is therefore employed in the titration of silver, with ferric sulphate as indicator; and it gives with ferric salts a dark blood-red coloration of **ammonium ferrithiocyanate**,  $2\text{Fe}(\text{CNS})_3$ ,  $9\text{NH}_4\text{CNS}$ ,  $4\text{H}_2\text{O}$ . This last reaction is exceedingly delicate. **Mercurous thiocyanate**,  $\text{HgCNS}$ , is a white powder insoluble in water, which increases enormously in volume upon being burnt (Pharaoh's serpents). The free **thiocyanic acid**,  $\text{CNSH}$ , as obtained by decomposing the mercurous salt with hydrochloric acid, is a pale-yellow liquid of pungent odour, but when pure is a colourless solid, m.-pt.  $5^\circ$ . The acid and its salts appear to have the normal structure  $\text{H}\cdot\text{S}\cdot\text{C}\cdot\text{N}$ . At the ordinary temperature it polymerizes to a yellow amorphous substance, and decomposes in concentrated aqueous solution, with formation of **persulphocyanic acid**,  $\text{C}_2\text{N}_2\text{S}_3\text{H}_2$  (yellow crystals).

Concentrated sulphuric acid decomposes the thiocyanates with formation of carbon oxy-sulphide:  $\text{CNSH} + \text{H}_2\text{O} \rightarrow \text{COS} + \text{NH}_3$ ; sulphuretted hydrogen decomposes them into carbon disulphide and ammonia:  $\text{CNSH} + \text{H}_2\text{S} = \text{CS}_2 + \text{NH}_3$ .

The alkyl derivatives of thiocyanic acid exist in two distinct forms, corresponding with the normal and iso-cyanates.

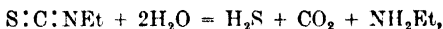
**Normal Thiocyanates.**—**Ethyl thiocyanate**,  $\text{N}:\text{C}\cdot\text{S}\cdot\text{CH}_2\cdot\text{CH}_3$ , is obtained either (1) by the distillation of potassium ethyl-sulphate with potassium thiocyanate, or (2) by the action of cyanogen chloride upon ethyl mercaptide. It is a colourless liquid with a peculiar pungent odour of leeks, boils at  $142^\circ$ , and is almost insoluble in water. Alcoholic potash hydrolyses it in the normal manner, yielding ethyl alcohol and potassium thiocyanate; in other reactions, however, the alkyl radical remains united to sulphur; thus nascent hydrogen

reduces it to mercaptan, and fuming nitric acid oxidizes it to ethyl-sulphonic acid.

These reactions, combined with its formation from a mercaptide, indicate that the ethyl group is directly attached to sulphur, viz.  $C_2H_5 \cdot S \cdot C : N$ .

**Allyl thiocyanate**,  $N : C \cdot S \cdot C_3H_5$ , is a colourless liquid smelling of leeks. It boils at  $161^\circ$ , and when distilled is converted into the isomeric mustard oil.

The **iso-thiocyanates** are usually known as mustard oils, and are more stable than the normal thiocyanates. They contain the alkyl radical attached to nitrogen, and not to sulphur (cf. Isocyanates), since on hydrolysis they yield primary amines, e.g.:



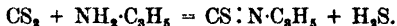
and also on reduction:



The thiomethylene formed in this last reaction immediately polymerizes to  $(CH_2S)_3$ . The commonest iso-thiocyanate is **allyl mustard oil**, commonly known as mustard oil, since the odour and taste of mustard seeds (*Sinapis niger*) are due to this compound. It does not exist as such in the seeds, but is formed from a glucoside, **potassium myronate**, when the seeds are pulverized and left in contact with water. The reaction is a process of fermentation, and is due to the presence of an enzyme, **myrosin**, in the seeds (Chap. LXIX, D.):



It is a liquid sparingly soluble in water and of exceedingly pungent odour, produces blisters on the skin, and boils at  $151^\circ$ . It is also obtained by distilling allyl thiocyanate, owing to a molecular rearrangement, or by the action of carbon disulphide upon allylamine:



This reaction proceeds in two stages, a dithiocarbamate,  $C_3H_5NH \cdot CS \cdot SNH_2 \cdot C_3H_5$ , the allylamine salt of allyl-dithiocarbamic acid being first formed, and this is changed into allyl iso-thiocyanate when distilled with mercuric chloride. (See Dithiocarbamic acid, Chap. XIII, D.)

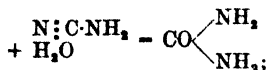
**Ethyl iso-thiocyanate**,  $C_2H_5N:CS$  (b.-pt.  $134^\circ$ ), and **methyl iso-thiocyanate**,  $CH_3N:CS$  (solid, m.-pt.  $34^\circ$ , b.-pt.  $119^\circ$ ), &c., closely resemble the allyl compound, and are obtained in an analogous manner by the action of carbon disulphide upon ethylamine, methylamine, &c.

The mustard oils are also obtained by distilling alkylated thio-ureas (Chap. XIII, D.) with syrupy phosphoric acid, or with concentrated hydrochloric acid.

## E. Cyanamide and its Derivatives

**The Amide of Cyanic Acid.**—Cyanamide,  $N:C\cdot NH_2$ , is formed by leading cyanogen chloride into an ethereal solution of ammonia,  $CNCl + 2NH_3 = CN\cdot NH_2 + NH_4Cl$ , or by the action of  $HgO$  upon thio-urea in aqueous solution ("desulphurization"),  $NH_2\cdot CS\cdot NH_2 = NC\cdot NH_2 + H_2S$ .

It is a colourless crystalline hygroscopic mass, readily soluble in water, alcohol, and ether. It melts at  $40^\circ$ , and when heated to  $150^\circ$  changes into the polymeric dicyan-diamide with explosive ebullition; the same change occurs on evaporating its solution or allowing it to stand. Dilute acids cause it to take up the elements of water, with formation of urea:



and it combines in an analogous manner with hydrogen sulphide to thio-urea. When heated with ammonium salts, it yields salts of guanidine.

Cyanamide behaves as a weak base, forming crystalline, easily decomposable salts with acids and, at the same time, as a weak acid, yielding a sodium salt,  $CN\cdot NHNa$ , a lead and a silver salt, &c. The last is a yellow powder, and has the composition  $CN_2Ag_2$ .

The calcium derivative of cyanamide,  $N:C\cdot NCa$ , is manufactured for use as a fertilizer, as, in the soil, the nitrogen becomes available for the plant in the form of ammonia. It is manufactured by passing air or nitrogen over calcium carbide at about  $800^\circ$ – $1000^\circ$ ,



or by passing nitrogen over a mixture of lime and carbon heated to  $2000^{\circ}$ . An excess of carbon is used, and the crude product, which forms a black powder, contains 14–23 per cent of nitrogen. The presence of a small amount of calcium chloride accelerates the absorption of nitrogen by calcium carbide.

For constitution cf. *Werner*, J. C. S., 1915, 715; also *Colson*, 1917, 554.

1. **Methyl-** and **ethyl-cyanamides** are prepared from methyl and ethyl thio-urea. **Diethyl-cyanamide**,  $\text{CN}_2(\text{C}_2\text{H}_5)_2$ , and its homologues are obtained by the action of alkyl iodides or sulphates on crude calcium cyanamide (B., 1911, 3149). Acids hydrolyse the ethyl compound to  $\text{CO}_2$ ,  $\text{NH}_3$ , and  $\text{NH}(\text{C}_2\text{H}_5)_2$ , hence it possesses the structure  $\text{N}:\text{C}:\text{N}(\text{C}_2\text{H}_5)_2$ :



2. Other cyanamide derivatives, which are chiefly known in the aromatic series, are derived from a hypothetical isomer of cyanamide, viz. carbo-di-imide,  $\text{NH}:\text{C}:\text{NH}$ ; for instance, **diphenyl-carbodiimide**,  $\text{C}(\text{NC}_6\text{H}_5)_2$ . Boiling with acids likewise decomposes them into  $\text{CO}_2$  and an amine, but the latter can only be a primary one.

### XIII. CARBONIC ACID DERIVATIVES

Carbonic acid is a dibasic acid, forming two series of salts, e.g.

$\text{Na}_2\text{CO}_3$  and  $\text{NaHCO}_3$ . The acid itself,  $\text{CO}_3\text{H}_2$ , =  $\text{O}:\text{C} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{OH} \end{array}$ ,

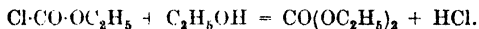
is unknown, but may be supposed to exist in the aqueous solution. It is the lowest hydroxy-acid  $\text{C}_n\text{H}_{2n}\text{O}_3$ , i.e. it is homologous with glycollic acid, and may be regarded as hydroxy-formic acid. As both hydroxyls are linked to the same carbon atom, the non-existence of the free hydrate is readily understood (see p. 146, &c.).

The salts of carbonic acid and several simple derivatives of carbon are usually treated of under inorganic chemistry. The esters, chlorides, and amides of carbonic acid, like the salts,

form two series. The **normal** compounds, e.g.  $\text{CO}(\text{OC}_2\text{H}_5)_2$ , ethyl carbonate,  $\text{COCl}_2$ , carbonyl chloride, and  $\text{CO}(\text{NH}_2)_2$ , carbamide or urea, are well characterized, and are very similar to those of oxalic or succinic acid; the **acid** compounds, e.g.  $\text{OH}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , ethyl hydrogen carbonate,  $\text{OH}\cdot\text{CO}\cdot\text{Cl}$ , chloroformic acid, and  $\text{OH}\cdot\text{CO}\cdot\text{NH}_2$ , carbamic acid, on the other hand, are unstable in the free state, but form stable salts. Many mixed derivatives are known, e.g. ethyl carbamate,  $\text{NH}_2\cdot\text{CO}\cdot\text{OEt}$ , which is an ester and an acid amide, analogous to ethyl oxamate (p. 271);  $\text{Cl}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , ethyl chloro-formate, which is an ester and an acid chloride.

### A. Esters

**Ethyl carbonate**,  $\text{CO}(\text{OC}_2\text{H}_5)_2$ , is formed by the action of ethyl iodide upon silver carbonate, or by the action of alcohol upon ethyl chloro-formate, and therefore indirectly from carbon oxy-chloride and alcohol:



It is a neutral liquid of agreeable odour, lighter than water, and boils at  $126^\circ$ .

Analogous **methyl** and **propyl esters** are known, and also esters containing two different alkyl groups. It is immaterial which alkyl is introduced first into the molecule, a proof of the symmetrical arrangement of the two hydroxyls.

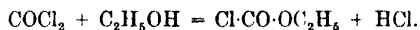
**Ethyl hydrogen carbonate**,  $\text{HO}\cdot\text{CO}\cdot\text{O}\cdot\text{C}_2\text{H}_5$ , a type of an acid ester, corresponds exactly with ethyl hydrogen sulphate, but is much less stable, and only known in its salts. **Potassium ethyl carbonate**,  $\text{KO}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , is obtained by passing  $\text{CO}_2$  into an alcoholic solution of potassic ethoxide:  $\text{CO}_2 + \text{KOC}_2\text{H}_5 = \text{CO}_3(\text{C}_2\text{H}_5)\text{K}$ . It crystallizes in glistening mother-of-pearl plates, but is decomposed by water into potassium carbonate and alcohol.

### B. Chlorides of Carbonic Acid

**Carbon oxy-chloride**, *Carbonyl chloride*, *phosgene*,  $\text{COCl}_2$  (*J. Davy*), is the true chloride of carbonic acid and is analogous to sulphuryl chloride,  $\text{SO}_2\text{Cl}_2$ . It is obtained by the direct combination of carbon monoxide and chlorine in sunlight, or

preferably in the dark with activated charcoal as catalyst at  $100^{\circ}$ – $125^{\circ}$ , and also by the oxidation of chloroform by means of chromic acid. It is a colourless gas, condensing to a liquid below  $+8^{\circ}$ , of exceptionally suffocating odour, and is readily soluble in benzene or toluene. As an acid chloride it decomposes violently with water into  $\text{CO}_2$  and  $\text{HCl}$ . It therefore transforms hydrated acids into their anhydrides, with separation of water, and converts aldehyde into ethylidene chloride. It yields urea derivatives with secondary amines of the fatty series, and carbamic chlorides with secondary amines of the aromatic. It is used as a poison gas and also for various syntheses.

**Chloro-formic acid**,\*  $\text{Cl}\cdot\text{CO}\cdot\text{OH}$ , the half acid chloride of carbonic acid, is analogous to the so-called chloroxalic acid (p. 268), but is so unstable that it is unknown in the free state. Its esters, however, e.g. **ethyl chloro-formate**,  $\text{Cl}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , may be prepared by the action of carbon oxy-chloride upon alcohols (*Dumas*, 1833):



The ethyl ester is a volatile liquid of very pungent odour, which boils at  $93^{\circ}$ . It reacts as an acid chloride, being decomposed by water, and is of synthetical value for introducing the carboxyl group into many compounds.

The esters and acid chlorides just described are derived from ordinary carbonic acid,  $\text{H}_2\text{CO}_3$ , the analogue of metasilicic acid,  $\text{H}_2\text{SiO}_3$ . Although an ortho-carbonic acid itself,  $\text{C}(\text{OH})_4$ , is unknown, certain derivatives are readily prepared. **Carbon tetrachloride** may be regarded as the chloride of ortho-carbonic acid. It is much more stable than ordinary acid chlorides, and at high temperatures only is it decomposed by alkalis, yielding alkali chloride and carbonate.

The esters of ortho-carbonic acid, e.g. **ethyl ortho-carbonate**,  $\text{C}(\text{OC}_2\text{H}_5)_4$ , are readily obtained by the action of sodium alcoholates on chloropierin (p. 107). They are colourless oils with fragrant odours. The **ethyl ester** boils at  $158^{\circ}$ , and the **propyl** at  $224^{\circ}$ . When hydrolysed, they yield an alkali carbonate and the alcohol.

\* Often erroneously called chlorocarbonic acid.

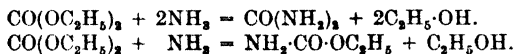
### C. Amides of Carbonic Acid

The normal amide of carbonic acid is **urea** or **carbamide**,  $\text{NH}_2\cdot\text{CO}\cdot\text{NH}_2$ , the amic acid is **carbamic acid**,  $\text{HO}\cdot\text{CO}\cdot\text{NH}_2$ . **Imido-carbonic acid**,  $\text{HN}:\text{C}(\text{OH})_2$ , would be an imide of carbonic acid, but it is only known in its derivatives (*Sandmeyer*).

The amidine of carbonic acid is **guanidine**. The "ortho-amide" of carbonic acid, which would possess the formula  $\text{C}(\text{NH}_2)_4$ , is unknown; when it might be expected, guanidine and ammonia are formed instead.

The modes of *formation* of urea and of carbamic acid are exactly analogous to those of the amides in general:

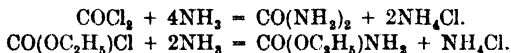
1. By the action of ammonia upon ethyl carbonate:



2. By the abstraction of the elements of water from carbonate or carbamate of ammonia. Dry carbon dioxide and ammonia combine together directly to ammonium carbamate the so-called anhydrous carbonate of ammonia,  $\text{NH}_2\cdot\text{CO}\cdot\text{ONH}_4$ , which is transformed into urea when heated to  $135^\circ$ , or when exposed to the action of an alternating current of electricity:



3. By the action of ammonia upon carbonyl chloride and its derivatives:



**Carbamic acid**,  $\text{NH}_2\cdot\text{CO}\cdot\text{OH}$ , is known only in the form of derivatives; the *ammonium* salt,  $\text{NH}_2\cdot\text{CO}\cdot\text{ONH}_4$ , forms a white mass, and dissociates at  $60^\circ$  into  $2\text{NH}_3 + \text{CO}_2$ . Its aqueous solution does not precipitate a solution of calcium chloride at the ordinary temperature; but when boiled it is hydrolysed to the carbonate, and calcium carbonate is then thrown down.

**Urethane**, *Ethyl carbamate*,  $\text{NH}_2\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$ , is formed according to method 3, and by the direct union of cyanic acid with alcohol; also from urea nitrate and sodium nitrite in presence of alcohol. It forms large plates, is readily soluble in water, melts at  $50^\circ$ , and boils at  $184^\circ$ . It acts



as a soporific, and on hydrolysis with alkali yields the alkali carbonate, ammonia and ethyl alcohol. One of its hydrogen atoms is replaceable by sodium. Urethane may be employed instead of cyanic acid for certain synthetic reactions. **Methyl** and **propyl esters** are also known.

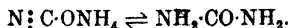
**Carbamic chloride**,  $\text{NH}_2\cdot\text{CO}\cdot\text{Cl}$ , obtained by the action of hydrogen chloride upon cyanic acid (*Wöhler*), and of carbonyl chloride upon ammonium chloride at  $400^\circ$ , forms long, compact, colourless needles of pungent odour. M.-pt.  $50^\circ$ , b.-pt.  $61^\circ\text{--}62^\circ$ . It reacts violently with water, amines, &c., and serves for the synthesis of organic acids (see these).

**Ethyl imido-dicarboxylate**,  $\text{NH}(\text{CO}_2\text{C}_2\text{H}_5)_2$ , is the imide corresponding with the amide urethane. It may be prepared from the sodium compound of urethane and ethyl chloroformate. It forms colourless crystals, melting at  $50^\circ$ . By the exchange of one ethoxy ( $\text{OC}_2\text{H}_5$ ) group for an amido ( $\text{NH}_2$ ) group, it gives rise to allophanic ester, and by the exchange of two, to biuret (see p. 327).

**Urea**, *Carbamide*,  $\text{CO}(\text{NH}_2)_2$ , was first found in urine in 1773. It is contained in the urine of mammals, birds, and some reptiles, and also in other animal fluids. An adult man produces about 30 gm. daily, and it may be regarded as the final decomposition product formed by the oxidation of the nitrogenous compounds in the organism.

It has been shown that ammonium cyanate and urea are formed when a very dilute solution of glucose (Chap. XIV, A.) in strong ammonia is oxidized. Larger yields are obtained by oxidizing an ammoniacal solution of formaldehyde. It is possible that this represents the changes which take place in the animal system, viz. glucose  $\rightarrow$  formaldehyde  $\rightarrow$  ammonium cyanate  $\rightarrow$  carbamide (*Fosse*, C. R., 1919, **168**, 164).

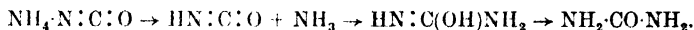
It may be prepared by the action of ammonia on ethyl carbonate, ethyl carbamate, or phosgene, and synthetically by the molecular transformation of ammonium cyanate, by warming its aqueous solution or allowing it to stand (cf. pp. 1 and 308):



The reaction is reversible, and hence the process is never complete. When equilibrium is reached, particularly in the presence of excess of ammonia, only a very small amount of untransformed cyanate is left, and the equilibrium is practically independent of the temperature. The reaction has been shown

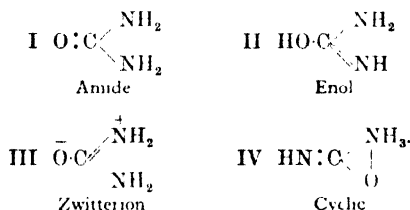
to be a typical bimolecular one (*Walker and Hamblly*, J. C. S., 1895, 746).

The reaction is represented as follows by *Chattaway* (J. C. S., 1912, 170. Compare also *Werner*, *ibid.* 1913, 1010, 2275; 1914, 926):



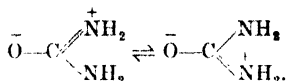
It is manufactured in Germany from  $\text{NH}_3$  and  $\text{CO}_2$ . It is also manufactured by the addition of water to cyanamide with the aid of dilute sulphuric acid, the removal of the acid by the addition of chalk and evaporation to dryness (C. and M. Eng., 1925, 791). It can also be obtained by the action of liquid  $\text{CO}_2$  on liquid ammonia and the process can be made continuous (J. I. E. C., 1930, 289).

Four different structures have been suggested for urea:



(Cf. *Taylor and Baker*, Org. Chem. of Nitrogen, Oxford, 1937; *Bergmann and Weizman*, Trans Far., 1938, 783.)

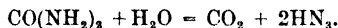
Dipole moment determinations point to III as the most probable structure for urea and also for thio-urea. In alkyl and particularly dialkyl-ureas and thio-ureas the tendency to ion formation is much less marked. The *Raman* effect points to the presence of the C:N group and X-ray examination points to a symmetrical structure, probably



It is interesting to note that when urea and its homologues are methylated by means of methyl sulphate O-methyl derivatives, e.g.  $\text{HN}:\text{C}(\text{NH}_2)\text{OMe}$ , are formed (*Werner*).

It crystallizes in long rhombic prisms or needles, has a cooling taste, is very readily soluble in water, also in alcohol, but not in ether. It melts at  $132^\circ$ , sublimes *in vacuo* without decomposition, and when strongly heated yields ammonia,

cyanuric acid, biuret, and ammeline. As an amide it is readily hydrolysed by boiling with alkalis or acids, or by superheating with water (cf. *Fawsitt*, J. C. S., 1904, 1581; 1905, 494):



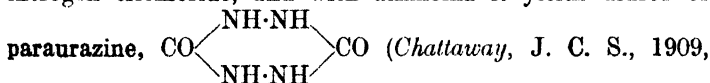
It forms a definite compound with hydrogen peroxide.

Nitrous acid reacts with it to produce carbon dioxide, nitrogen, and water:



Sodium hypochlorite and hypobromite act in a similar manner (*Davy*, *Knop*), and *Hüfner's* method of estimating urea quantitatively depends upon the measurement of the nitrogen evolved. Urea also reacts with bromine and alkalis in much the same manner as the lower acid amides (*Hofmann* reaction, p. 211 and Chap. XXXVIII), yielding carbon dioxide and the corresponding amine, hydrazine (C. Z., 1905, i, 1227), which is best removed by the addition of benzaldehyde. Urea is readily estimated by conversion into ammonia, either by heating with pure crystallized magnesium chloride and a little hydrochloric acid or by means of an enzyme (a urease) contained in soya beans.

Urea reacts with an aqueous solution of chlorine, yielding the dichloro-derivative  $\text{CO}(\text{NHCl})_2$ . With acids this forms nitrogen trichloride, and with ammonia it yields diurea or



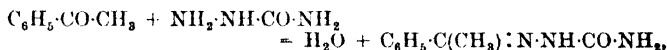
129, 235). When warmed with alcoholic potash to  $100^\circ$ , urea is converted into cyanate of potassium and ammonia.

The basic character of the amino groups is greatly weakened in urea by the presence of the negative carbonyl. Among the salts of urea with acids may be mentioned **urea nitrate**,  $\text{CON}_2\text{H}_4 \cdot \text{HNO}_3$ , which crystallizes in glistening white plates, readily soluble in water, but only slightly in nitric acid; also the **chloride**, **oxalate**, and **phosphate**. But like acetamide, urea also forms salts with metallic oxides, especially with mercuric oxide, e.g.  $\text{CON}_2\text{H}_4 \cdot 2\text{HgO}$ ; finally, it yields crystalline compounds with salts, e.g. **urea sodium chloride**,  $\text{CON}_2\text{H}_4 \cdot \text{NaCl} \cdot \text{H}_2\text{O}$  (glistening prisms), and **urea silver nitrate**,  $\text{CON}_2\text{H}_4 \cdot \text{AgNO}_3$  (rhombic prisms). The precipitate which is obtained on adding mercuric nitrate to a neutral aqueous

solution of urea has the formula  $2\text{CON}_2\text{H}_4$ ,  $\text{Hg}(\text{NO}_3)_2$ ,  $3\text{HgO}$  and upon its formation depends *Liebig's* method for titrating urea.

Isomeric with urea is the amidoxime, **isuret** or methane amidoxime,  $\text{NH}:\text{CH}\cdot\text{NH}\cdot\text{OH}$ , which is obtained from  $\text{HCN}$  and  $\text{NH}_2\text{OH}$ ; it crystallizes in prisms (see p. 217).

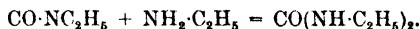
Closely related to carbamide,  $\text{NH}_2\cdot\text{CO}\cdot\text{NH}_2$ , is **semicarbazide** or semihydrocarbazide,  $\text{NH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{NH}_2$ , which is the half amide and half hydrazide of carbonic acid. It may be prepared from potassium cyanate and hydrazine hydrate. It is a basic substance, melts at  $96^\circ$ , and is usually met with in the form of its hydrochloride. It reacts with aldehydes and ketones in much the same manner as phenyl-hydrazine, yielding condensation products known as **semicarbazones**:



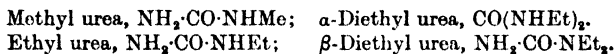
which crystallize well, and have well-defined melting-points (see p. 160).

**Alkylated ureas** are obtained by the exchange of the amidohydrogen atoms for one or more alkyl radicals.

They are produced by *Wöhler's* synthetical method, viz. by the combination of cyanic acid with amines, or of cyanic esters with ammonia or amines, thus:



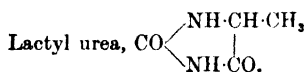
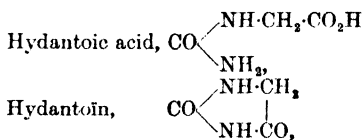
Also from amines and carbon oxy-chloride. As examples may be mentioned:



Certain of them closely resemble urea; others, however, are liquid and volatilize without decomposition. Their *constitution* follows very simply from the nature of the products which are formed on hydrolysis; thus  $\alpha$ -diethyl urea breaks up into carbon dioxide and ethylamine, and the  $\beta$ -compound into carbon dioxide, ammonia, and diethylamine, in accordance with the generalization enunciated on p. 114, that alkyl radicals which are directly united to nitrogen are eliminated as amines on hydrolysis.

**Acyl Derivatives.**—By the entrance of acyl radicals into urea, its acid derivatives or **ureides** are formed. These are formed by the action of acid chlorides or anhydrides upon

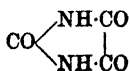
urea, or by the action of phosphorus oxy-chloride upon the salts of urea with organic acids. The simple ureides correspond in many respects with acid amides or anilides, have neither distinctly acid nor basic properties, and may be hydrolysed to the acid and urea or its products of decomposition (p. 320). To this class belong **acetyl urea**,  $\text{NH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ , and **allophanic acid**,  $\text{NH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}_2\text{H}$ . Hydroxy-monobasic acids also form ureides, not only in virtue of their acidic nature, but as alcohol and acid at the same time, thus:



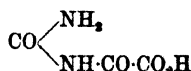
**Hydantoin** or *glycolyl urea* (needles, neutral) and **hydantoic acid** or *glycoluric acid* (prisms), are derivatives of glycollic acid; the former on hydrolysis yields hydantoic acid, which in its turn is broken up into  $\text{CO}_2$ ,  $\text{NH}_3$ , and glycocoll. They are obtained from certain uric acid derivatives (e.g. allantoin) by the action of hydriodic acid, and also synthetically, for instance, hydantoic acid from glycocoll and cyanic acid. A **methyl-hydantoin**,  $\text{C}_3\text{H}_3(\text{CH}_3)\text{N}_2\text{O}_2$ , results from the partial hydrolysis of creatinine (p. 335),  $\text{NH}$  being replaced by  $\text{O}$ .

Numerous substituted hydantoins are formed by the action of hypochlorites or hypobromites on dialkylated malonamides, e.g. diethylmalonamide,  $\text{C}_2\text{H}_5\text{CONH}_2$ , gives diethylhydantoin, and by other methods (cf. Thorpe's Dic., II, 633).

Just as the dibasic acids—oxalic, malonic, tartaric, and mesoxalic—yield amides with ammonia, so with urea they form compounds of an amidic nature. In such reactions either two molecules of water are eliminated, so that no carboxyl remains in the compound, or only one molecule is eliminated and a carboxyl group is retained. In the former case the so-called **cyclic ureides** are obtained, and in the latter the **ureido-acids**, e.g. from oxalic acid, parabanic and oxaluric acids:



Cyclic ureide (parabanic acid)

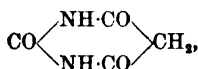


Ureido-acid (oxaluric acid)

In an analogous manner the ureide barbituric acid,  $C_4H_4N_2O_3$ , is derived from malonic acid, the ureide dialuric acid,  $C_4H_4N_2O_4$ , from tartronic acid, and the ureide alloxan,  $C_4H_2N_2O_4$ , and ureido-acid alloxanic acid,  $C_4H_4N_2O_5$ , from mesoxalic acid. These are solid and, for the most part, beautifully crystallizing compounds of a normal amidic character, and therefore readily hydrolysed to urea (or  $CO_2$  and  $NH_3$ ) and the respective acid. The ureido-acids may be regarded as half-hydrolysed ureides, and may be prepared from the latter in this manner. As they contain a carboxyl group, they still possess acidic properties.

The constitution of the various cyclic ureides and ureido-acids follows in most cases from the products they yield on hydrolysis, and also from their synthetical methods of formation and their relationships to one another.

Some of these ureides are obtained synthetically from urea and the requisite acid often in the presence of phosphorus oxy-chloride, e.g. malonyl-urea (barbituric acid),



from urea and malonic acid. Many can be obtained by the oxidation of various complex natural products, e.g. alloxan or parabanic acid by oxidizing uric acid with nitric acid.

Most of the ureides have the character of moderately strong acids. Since this acid character is not to be explained, as in the case of the ureido-acids, by the presence of carboxyl groups, it is probably due to the presence of NH groups attached to CO. This explains, for instance, why parabanic acid is a strong dibasic acid.

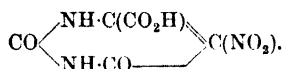
Only a few of the more important among these compounds can be discussed here. The names given to the majority of them have no relationship to their constitution, and were assigned to them before the constitutions had been determined.

**Parabanic acid, Oxalyl urea,**  $\begin{array}{c} \text{NH} \cdot \text{CO} \\ \text{CO} \diagup \quad \diagdown \\ \text{NH} \cdot \text{CO} \end{array}$ , is prepared

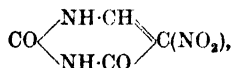
by the action of nitric acid upon uric acid, or of oxalyl chloride on urea, and crystallizes in needles or prisms soluble in water and alcohol. The salts, e.g.  $C_3HKN_2O_5$ ,  $C_3Ag_2N_2O_5$ , are unstable, being converted by water into salts of oxaluric acid,  $NH_2 \cdot CO \cdot NH \cdot CO \cdot CO_2H$ , which crystallize well.

A methyl-parabanic acid,  $\text{CO} \begin{array}{l} \text{NMe} \cdot \text{CO} \\ \text{NH} - \text{CO} \end{array}$ , and a dimethyl-parabanic acid, the so-called "cholestophane",  $\text{CO} \begin{array}{l} \text{NMe} \cdot \text{CO} \\ \text{NMe} \cdot \text{CO} \end{array}$ , are also known. The former is prepared by the action of nitric acid upon methyl-uric acid, and crystallizes in prisms, while the latter is obtained from theine with nitric acid or chlorine water, and also by the methylation of parabanic acid, i.e. from the silver salt and methyl iodide. It crystallizes in plates and distills without decomposition.

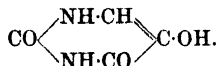
Methyl-uracyl,  $\text{CO} \begin{array}{l} \text{NH} \cdot \text{C}(\text{CH}_3) \\ \text{NH} \cdot \text{CO} \end{array} \text{CH}$ , is produced by the action of urea upon acetoacetic ester, water and alcohol being eliminated. When it is treated with nitric acid, a nitro-group enters the molecule, and the methyl group is oxidized to carboxyl, thus forming 5-nitro-uracyl-4-carboxylic acid,



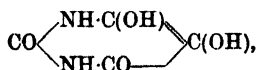
This in its turn can give up carbon dioxide and pass into 5-nitro-uracyl,



which yields upon reduction with tin and hydrochloric acid 5-amino-uracyl and isobarbituric acid, 5-hydroxy-uracyl,



This last is oxidized by bromine water to isodialuric acid,



from which uric acid may be synthesized by warming with urea and sulphuric acid (see p. 328).

**Barbituric acid, Malonyl urea**,  $\text{CO} \begin{array}{c} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{CH}_2$ , crystallizes in large colourless prisms ( $+2\text{H}_2\text{O}$ ) ( $K \times 10^5 = 10$ ). The hydrogen atoms of the methylene group are reactive (cf. ethyl malonate), and can be replaced by bromine,  $\cdot\text{NO}_2$ ,  $\cdot\text{N} \cdot \text{OH}$ , metals, &c. The metallic radicals in their turn can be replaced by alkyl groups. The dimethyl derivative when hydrolysed yields carbon dioxide, ammonia, and dimethylmalonic acid, thus indicating that the methyl groups have replaced the methylene hydrogen atoms. The *iso*-nitroso derivative,  $\text{CO} \begin{array}{c} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{C} : \text{N} \cdot \text{OH}$ , **violuric acid**, can also

be obtained by the action of hydroxylamine on alloxan, and on reduction yields **amino-barbituric acid** (uramil), from which pseudouric and uric acids have been synthesized (p. 328). **Diethylbarbituric acid** (*veronal* or *barbital*) and **Ethylphenylbarbituric acid**,  $\text{CO}(\text{NH} \cdot \text{CO})_2\text{C} \cdot \text{EtPh}$ , *luminal* are used as soporifics, and yield metallic (sodium) derivatives used for the same purpose.

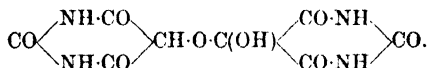
**Dialuric acid, Tartronyl urea**,  $\text{CO} \begin{array}{c} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{CH} \cdot \text{OH}$ , crystallizes in colourless needles or prisms which redden in the air. It is a strong dibasic acid, and on oxidation yields alloxantin.

**Alloxan, Mesoxalyl urea**,  $\text{CO} \begin{array}{c} \text{NH} \cdot \text{CO} \\ \text{NH} \cdot \text{CO} \end{array} \text{CO}$ , may be prepared from uric acid by oxidation with cold  $\text{HNO}_3$ . It forms large colourless glistening rhombic prisms ( $+4\text{H}_2\text{O}$ ), is readily soluble in water, and has strongly acidic properties. It colours the skin purple-red, and with ferrous sulphate solution produces an indigo-blue colour. It combines with  $\text{NaHSO}_3$ , and readily changes into alloxantin. The corresponding ureido-acid, **alloxanic acid**,  $\text{NH}_2 \cdot \text{CO} \cdot \text{NH} \cdot \text{CO} \cdot \text{CO} \cdot \text{CO}_2\text{H}$ , which alloxan yields even with cold alkali, forms a radiating crystalline mass readily soluble in water. **Methyl- and di-methyl-alloxan** are also known, and may be obtained by the action of nitric acid upon methyl-uric acid and caffeine respectively.

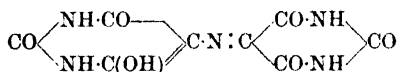
The diureide **alloxantin**,  $\text{C}_8\text{H}_4\text{O}_7\text{N}_4$ , stands midway in



composition between tartronyl- and mesoxalyl-urea, by the combination of which it is formed. It may also be obtained by the action of  $\text{H}_2\text{S}$  on alloxan, or directly from uric acid and  $\text{HNO}_3$ . It crystallizes in small hard prisms ( $+3\text{H}_2\text{O}$ ), which become red in air containing ammonia, their solution acquiring a deep-blue colour on the addition of ferric chloride and ammonia. The tetramethyl derivative, **amalic acid**,  $\text{C}_8(\text{CH}_3)_4\text{N}_4\text{O}_7$ , is obtained by oxidizing theine with chlorine water, and forms colourless crystals which redden the skin and whose solution is turned violet-blue by alkali. Both these compounds yield, upon oxidation, first alloxan or its dimethyl derivative, and then parabanic or dimethyl-parabanic acid. Alloxantin probably has the constitution:

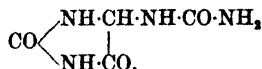


When heated with ammonia it is converted into **murexide**, the acid ammonium salt of **purpuric acid**,  $\text{C}_8\text{H}_5\text{N}_6\text{O}_6$ ; this is the acid form of barbituryl iminoalloxan:



(J. pr., 1905 [ii], 73, 449), which is formed when uric acid is evaporated with dilute nitric acid, and ammonia added to the residue; this constitutes the "**murexide test**" for uric acid. Murexide crystallizes in four-sided plates or prisms ( $+\text{H}_2\text{O}$ ) of a golden-green colour, which dissolve to a purple-red solution in water and to a blue one in potash. The free acid is incapable of existence.

**Allantoin** is a diureide of glyoxylic acid, of the constitution

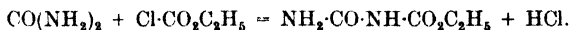


and is found in the allantoinic liquid of the cow, the urine of sucking calves, &c. It forms glistening prisms, and can be synthesized from its components.

**Biuret**,  $\text{NH}_2\text{-CO-NH-CO-NH}_2$ , is obtained by heating urea at  $160^\circ$  (for mechanism cf. *Werner*, J. C. S., 1913, 2278).



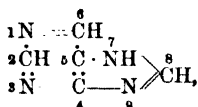
It crystallizes in white needles ( $+H_2O$ ), and is readily soluble in water and alcohol. The alkaline solution gives a beautiful violet-red coloration on the addition of a little cupric sulphate—the “**biuret reaction**”. Biuret is also formed by the action of ammonia upon the **allophanic esters**, crystalline compounds sparingly soluble in water, which are prepared from urea and chloro-carbonic esters, thus:



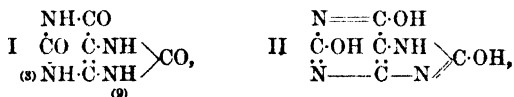
Allophanic acid itself is not known in the free state, as it immediately breaks up into urea and carbon dioxide. Biuret may be regarded as its amide.

**The Purine Group** (*E. Fischer*, B., 1899, 435; 1902, 2564).—A number of relatively complex cyclic diureides derived from 1 molecule of hydroxy dibasic acids and 2 of urea are known. One of the most important of these is **uric acid**.

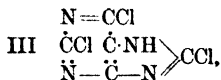
The parent substance of this group of compounds is purine. Purine:



is usually obtained from uric acid I, which reacts with phosphorus oxy-chloride as the tautomeric trihydroxy purine II:



yielding the corresponding trichlorpurine III:



and this on reduction yields purine itself. It is a colourless crystalline compound, melts at  $217^\circ$ , and is both an acid and a base. It dissolves readily in water, and is not easily oxidized. The atoms of the ring are usually numbered as indicated.

**Uric acid** is the keto form of 2 : 6 : 8-*trihydroxy-purine*, and has the constitutional formula I above.

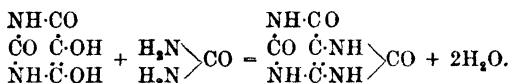
Uric acid and many other compounds containing the  $\cdot\text{NH} \cdot \text{CO} \cdot$  group, as tautomeric substances, behave in certain

reactions as ketonic compounds and in other reactions as hydroxylic derivatives, i.e. they exhibit keto-enolic tautomerism.

It is a common constituent of the urine of most carnivorous animals, whereas that of herbivorous animals contains hippuric acid. The average human excretes about 0.6 gm. per diem. It is also found in the blood and muscle juices of the same animals. Human blood contains about 30 mg. per litre, and is the oxidation product of the nucleic acids of food and the nucleo-proteins of the tissues. These give rise to the four purine bases guanine (2-amino-6-oxy-) adenine (6-amino-) hypoxanthine (6-oxy-) and xanthine (2:6-dioxy-purine). It is also contained in the excrement of birds, serpents, and insects, and in guano.

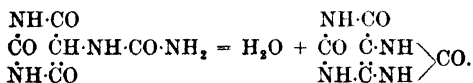
*Syntheses*.—1. By heating glycocoll with urea (*Horbaczewski*, B., 1882, 2678).

2. By heating isodialuric acid (p. 325) with urea and concentrated sulphuric acid (*R. Behrend* and *O. Roosen*, A., 251, 235):

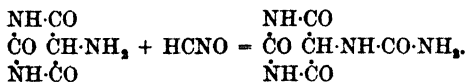


3. By heating cyano-acetic acid with urea (*Traube*, B., 1891, 3419; 1900, 3035).

4. By heating pseudouric acid with hydrochloric acid when water is eliminated (*E. Fischer*, B., 1897, 559):



The pseudo acid is obtained as the potassium salt by the condensation of amino-barbituric acid (p. 325) with potassium cyanate (*Baeyer*):



It is usually prepared from guano and the excrement of serpents, and crystallizes in small plates; is almost insoluble in water, and quite insoluble in alcohol or ether. Uric acid is a weak dibasic acid; its common salts are the acid ones, replacement of H in (3) and then in (9), e.g.  $\text{C}_5\text{H}_3\text{O}_3\text{N}_4\text{K}$ , a

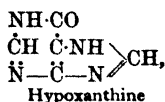
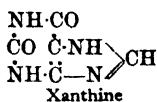
powder sparingly soluble in water. The lithium and piperazine salts are somewhat more soluble, and hence are used in medicine for removing uric acid from the human system. The accumulation of uric acid in the system produces various diseases: gout due to deposition of the acid in the joints, stones in bladder, kidneys, &c., due to formation of the solid crystals, different types of rheumatism, &c.

When the two lead salts are treated with methyl iodide, **methyl-** and **dimethyl uric acids** are obtained, both of which are weak dibasic acids, since they still contain replaceable imido-hydrogen atoms.

*Constitution.*—The constitutional formula, given above, was first proposed by *Medicus*, and afterwards proved to be correct by *E. Fischer* (A., 215, 253). The more important arguments used were: (1) Uric acid yields alloxan and urea when cautiously oxidized, indicating that it contains the 6 membered pyrimidine ring condensed with a carbonic acid derivative. Another product formed on oxidation is parabanic acid, thus proving the presence of the 5 membered iminazole ring; (2) uric acid contains four imido groups, since, by the introduction of four methyl groups, one after the other, four mono-methyl, various di- and trimethyl, and one tetramethyl uric acids are obtained. When the tetramethyl acid is hydrolysed with concentrated hydrochloric acid all the nitrogen is eliminated as methylamine, and thus each methyl group is probably attached to a nitrogen atom; (3) dimethyluric acid yields methylalloxan and methylurea on oxidation.

Uric acid is usually recognized by its sparing solubility, and by its giving the murexide test.

**Xanthine**, 2 : 6-*Dihydroxy-purine*, or the corresponding keto form:



may be obtained by the reduction of uric acid with sodium amalgam, or by the action of nitrous acid on guanine (2-amino-6-oxypurine). It is a white amorphous mass, and is both basic and acidic. The lead salt,  $\text{C}_5\text{H}_2\text{PbN}_4\text{O}_2$ , is converted into theobromine by methyl iodide. (Cf. B., 1897, 2235; 1900, 3035.) When oxidized it yields the same products as uric acid.

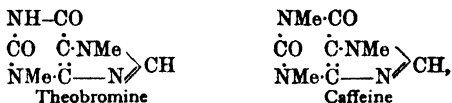
# PRODUCTS OBTAINABLE FROM URIC ACID

1. ON OXIDATION		2. ON REDUCTION	3. WITH $\text{PCl}_5$
<p>(a)</p> <p>With dilute <math>\text{HNO}_3</math>,  <math>\downarrow</math>  <math>\text{Alloxan, CO} \begin{array}{c} \text{NH} \cdot \text{CO} \\ \diagup \quad \diagdown \end{array} \text{CO,}</math>  <math>\downarrow</math> reduced.  <math>\text{Dialuric acid,}</math>  <math>\text{NH} \cdot \text{CO} \begin{array}{c} \text{CH} \cdot \text{OH}, \\ \diagup \quad \diagdown \end{array}</math>  <math>\downarrow</math> reduced.  <math>\text{Barbituric acid}</math>  <math>\text{CO} \begin{array}{c} \text{NH} \cdot \text{CO} \\ \diagup \quad \diagdown \end{array} \text{CH}_3,</math>  <math>\text{Alloxan and dialuric acid give}</math>  <math>\text{alloxantin,}</math>  <math>\text{CO} \begin{array}{c} \text{NH} \cdot \text{CO} \\ \diagup \quad \diagdown \end{array} \text{C} \cdot \text{C} \begin{array}{c} \text{CO} \cdot \text{NH} \\ \diagup \quad \diagdown \end{array} \text{CO,}</math>  <math>\text{NH} \cdot \text{CO} \begin{array}{c} \text{NH} \cdot \text{CO} \\ \diagup \quad \diagdown \end{array} \text{O}</math></p>	<p>(b)</p> <p>With concentrated <math>\text{HNO}_3</math>,  <math>\downarrow</math>  <math>\text{Parabanic acid,}</math>  <math>\text{NH} \cdot \text{CO} \begin{array}{c} \text{NH} \cdot \text{CO}_2 \\ \diagup \quad \diagdown \end{array}</math>  <math>\downarrow</math> with <math>\text{KOH.}</math>  <math>\text{Oxaluric acid,}</math>  <math>\text{NH} \cdot \text{CO} \cdot \text{COOH}</math>  <math>\text{CO} \begin{array}{c} \text{NH}_2 \\ \diagup \quad \diagdown \end{array}</math></p>	<p>(c)</p> <p>In alkaline solution  <math>\downarrow</math>  <math>\text{Allantoin,}</math>  <math>\text{NH} \cdot \text{CH} \cdot \text{NH} \cdot \text{CO} \cdot \text{NH}_2</math>  <math>\downarrow</math> reduced.  <math>\text{Hydantoin,}</math>  <math>\text{NH} \cdot \text{CH}_2 \begin{array}{c} \text{NH} \cdot \text{CO} \\ \diagup \quad \diagdown \end{array}</math>  <math>\downarrow</math>  <math>\text{Hydrolysed}</math>  <math>\text{Allantoic acid,}</math>  <math>\text{NH} \cdot \text{CH}_2 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH}_2</math>  <math>\text{CO} \begin{array}{c} \text{NH} \cdot \text{CO}_2 \text{H.} \\ \diagup \quad \diagdown \end{array}</math></p>	<p>Trichloro-purine,  <math>\downarrow</math> reduced,  <math>\text{Purine,}</math>  <math>\text{N} = \text{CH}</math>  <math>\text{CH} \cdot \text{C} \cdot \text{NH} \begin{array}{c} \text{CH.} \\ \diagup \quad \diagdown \end{array}</math>  <math>\text{N} - \text{C} - \text{N}</math>  <math>\text{Xanthine, hypo-}</math>  <math>\text{xanthine, guan-}</math>  <math>\text{ine, and adenine}</math>  <math>\text{can also be ob-}</math>  <math>\text{tained from tri-}</math>  <math>\text{chloro - purine}</math>  <math>\text{(B., 1897, 2220,}</math>  <math>\text{2226).}</math></p>

For details of oxidation with hydrogen peroxide cf. Venable and others, J. A. C. S., 1917, 1750; 1918, 1099, 1120.

**Hypoxanthine**, *Sarcine*, or 6-oxy-purine, is sparingly soluble in water and closely resembles xanthine.

**Theobromine**, 3 : 7-Dimethyl-xanthine,



occurs in the beans of cacao; it is a crystalline powder of bitter taste, and is only sparingly soluble in water and alcohol. It forms salts both as a base and as an acid. The silver salt,  $\text{C}_7\text{H}_7\text{AgN}_4\text{O}_2$ , when treated with  $\text{CH}_3\text{I}$ , yields **caffeine** or **theine**, 1 : 3 : 7-trimethyl-xanthine, which occurs in tea (2-4 per cent), coffee, and various plants. (For synthesis from dimethyl urea and malonic acid see *Fischer*, B., 1895, 3137; 1899, 435; from cyanoacetic acid, 1900, 3035.) It crystallizes (+  $\text{H}_2\text{O}$ ) in beautiful long glistening silky needles of faintly bitter taste, which are sparingly soluble in cold water and alcohol, and can be sublimed. The salts are readily decomposed by water. Chlorine oxidizes it to dimethyl-alloxan and monomethyl-urea. **Theophylline**, 1 : 3-dimethyl-xanthine, also occurs in tea.

**Guanine**, 2-amino-6-oxy-purine, or 2-amino-hypoxanthine, and **adenine**, 6-amino-purine, both contain amino-groups, and are thus basic substances. Both compounds, together with xanthine and hypoxanthine, are formed by the decomposition of the nucleic acids and other complex compounds contained in the animal system. The constitution follows largely from (1) basic properties, (2) their conversion respectively into xanthine and hypoxanthine by the aid of nitrous acid, and (3) from their oxidation products.

A summary of some of the more important ureides which can be obtained from uric acid are tabulated on p. 330.

For other uric acid derivatives cf. *Biltz*, A., 1916, **413**, 1-206; 1917, **414**, 54.

## D. Sulphur Derivatives of Carbonic Acid

In addition to most of the carbonic acid derivatives which have been described, there exist analogous compounds in which the oxygen is wholly or partially replaced by sulphur. Many of these again are unstable in the free state, from the fact of their being too readily hydrolysed to  $\text{CO}_2$ ,  $\text{COS}$ , or  $\text{CS}_2$ , but

they are known as salts, or at least as esters. Some of the latter are sulphur esters, e.g.  $\text{CO}(\text{SEt})_2$ , and as such on hydrolysis yield mercaptans and not alcohols.

Various mono-, di-, and tri-thio-derivatives of carbonic acid are known, according as 1, 2, or 3 of the oxygen atoms are replaced by sulphur.

Many of the thio-acids react as tautomeric substances, and give rise to isomeric alkyl derivatives in exactly the same manner as hydrocyanic, cyanic, and thiocyanic acids.

**Thiophosgene, Thiocarbonyl chloride,  $\text{CSCl}_2$ .** When chlorine is allowed to act upon carbon disulphide, there is first formed the compound  $\text{CCl}_3\cdot\text{SCl}$ , which is converted into thiophosgene by  $\text{SnCl}_2$ . It is a red, mobile, strongly fuming liquid of sweetish taste, which attacks the mucous membrane, and boils at  $73^\circ$ . In its chemical behaviour it closely resembles phosgene, but is much more stable towards water than the latter, being only slowly decomposed even by hot water. With ammonia it yields ammonium thiocyanate and not thiocarbamide.

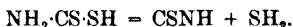
**Thiocarbonic Acids.**—Tri-thiocarbonic acid is made up of the constituents  $\text{CS}_2 + \text{H}_2\text{S}$ , so that carbon disulphide is its thio-anhydride, while the di-thiocarbonic acids contain the elements of  $\text{CS}_2 + \text{H}_2\text{O}$  or of  $\text{COS} + \text{H}_2\text{S}$ , and the mono-acids those of  $\text{COS} + \text{H}_2\text{O}$  or of  $\text{CO}_2 + \text{H}_2\text{S}$ . We find accordingly that  $\text{CS}_2$  combines with  $\text{Na}_2\text{S}$  to  $\text{CS}_3\text{Na}_2$ , sodium tri-thiocarbonate, with  $\text{KSC}_2\text{H}_5$  to  $\text{CS}(\text{SC}_2\text{H}_5)\text{SK}$ , with  $\text{KOC}_2\text{H}_5$  (i.e. an alcoholic solution of potash) to  $\text{CS}(\text{OC}_2\text{H}_5)\text{SK}$ , potassium xanthate. In a similar manner  $\text{COS}$  and  $\text{CCl}_4$  combine with mercaptides and alcoholates.

**Tri-thiocarbonic acid,  $\text{CS}_3\text{H}_2$ ,** is a brown oil, insoluble in water, and readily decomposed, and its **ethyl ester,  $\text{S}:\text{C}(\text{SC}_2\text{H}_5)_2$ ,** a liquid boiling at  $240^\circ$ .

**Potassium xanthate,  $\text{S}:\text{C} \begin{array}{l} \nearrow \text{OC}_2\text{H}_5 \\ \searrow \text{SK} \end{array}$ ,** obtained by the action

of potassium ethoxide,  $(\text{KOH} + \text{C}_2\text{H}_5\text{OH})$ , on carbon disulphide, crystallizes in beautiful colourless needles, very readily soluble in water, less so in alcohol. A solution of cupric sulphate throws down cupric xanthate as a yellow unstable precipitate, hence the name. It is employed in indigo printing. The free **xanthic acid, ethyl hydrogen di-thiocarbonate,  $\text{S}:\text{C}(\text{OEt})\cdot\text{SH}$ ,** is an oil insoluble in water, and decomposes at so low a temperature as  $25^\circ$  into carbon disulphide and alcohol.

**Thiocarbamic Acids.**—**Di-thiocarbamic acid**,  $\text{NH}_2\cdot\text{CS}\cdot\text{SH}$ , is formed as ammonium salt by the combination of  $\text{CS}_2$  and  $\text{NH}_3$  in alcoholic solution:  $\text{CS}_2 + 2\text{NH}_3 = \text{NH}_2\cdot\text{CS}\cdot\text{SNH}_4$ . The free acid is a reddish oil which easily decomposes into thiocyanic acid and sulphuretted hydrogen:



Carbon disulphide combines in an analogous manner with primary amines to form the amine salts of alkylated di-thiocarbamic acids; thus ethylamine yields **ethylamine ethyl-di-thiocarbamate**,  $\text{C}_2\text{H}_5\text{NH}\cdot\text{CS}\cdot\text{SNH}_3\text{C}_2\text{H}_5$ . When such salts are heated above  $100^\circ$ ,  $\text{H}_2\text{S}$  is evolved and a dialkyl-thio-urea left behind, e.g. **diethyl-thio-urea**,  $\text{CS}(\text{NHC}_2\text{H}_5)_2$ ; when  $\text{HgCl}_2$  or  $\text{AgNO}_3$  is added to their solutions, the Hg or Ag salts of the acids are precipitated, and these decompose on boiling with water into  $\text{HgS}$  or  $\text{Ag}_2\text{S}$  and the corresponding mustard oil (cf. p. 312):



Secondary amines also give rise to alkylated di-thiocarbamic acids, but the latter do not yield mustard oils.

**Thiocarbamide**, *Thio-urea*, *sulpho-urea*,  $\text{S}:\text{C}(\text{NH}_2)_2$  (*Reynolds*), is the analogue of urea, and its *modes of formation* are exactly similar to those of the latter. Thus it is formed from ammonium thiocyanate just as urea is from the cyanate.

To effect this molecular transformation a temperature of at least  $130^\circ$  is required, and it is only partial, as the reaction is reversible. At  $170^\circ$  equilibrium is attained after 45 minutes, and the mixture then contains only 25 per cent of thiocarbamide (*Reynolds* and *Werner*, P., 1902, 207). It may also be formed by the direct union of sulphuretted hydrogen with cyanamide:



Thiocarbamide crystallizes in rhombic six-sided prisms, or—if not quite pure—in long silky needles, readily soluble in water and alcohol. M.-pt.  $172^\circ$ . It is easily hydrolysed to  $\text{CO}_2$ ,  $\text{H}_2\text{S}$ , and  $2\text{NH}_3$ .  $\text{HgO}$  abstracts  $\text{H}_2\text{S}$  from it, with formation of cyanamide. Cold permanganate of potash solution oxidizes it to urea. As a weak base it forms salts with strong acids, but also yields salts with  $\text{HgO}$  and other metallic oxides; it also combines with salts, such as  $\text{AgCl}$ ,  $\text{PtCl}_4$ , &c. When



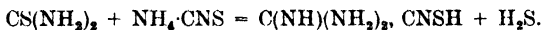
heated with alcoholic potash to  $100^{\circ}$ , it is reconverted into (the potassium salt of) thiocyanic acid and ammonia.

Thiocarbamide gives rise to alkyl derivatives (normal and pseudo), acyl derivatives, cyclic ureides, &c., in much the same manner as urea itself. For structure cf. p. 319.

### E. Amidines of Carbonic Acid

**Guanidine**, or **Imino-carbamide**,  $\text{NH}:\text{C}(\text{NH}_2)_2$ , (*Strecker*, 1861), may be obtained by the oxidation of guanine, also by heating cyanamide and ammonium iodide, and therefore from cyanogen iodide and ammonia,  $\text{CN}\cdot\text{NH}_2 + \text{NH}_4\text{I} = \text{CN}_3\text{H}_5, \text{HI}$ .

It is usually prepared as isothiocyanate by heating thio-urea with ammonium thiocyanate to  $180^{\circ}$ – $190^{\circ}$  (*Volhard*):

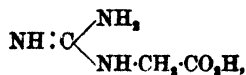


The perchlorate is formed by the action of ammonium perchlorate on dicyanodiamide. Alkylated guanidines are formed by the action of an alkylamine hydrochloride on dicyanodiamide,  $\text{C}_2\text{H}_4\text{N}_4$ , *Werner and Bell* (*J. C. S.*, 1922, 1790).

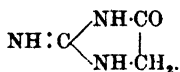
Guanidine crystallizes well, is readily soluble in water and alcohol, deliquesces in the air, and is a sufficiently strong monoacid base to absorb carbon dioxide. **Guanidine carbonate**,  $(\text{CN}_3\text{H}_5)_2, \text{H}_2\text{CO}_3$ , crystallizes beautifully in quadratic prisms. The base is readily hydrolysed, at first to urea and ammonia, and finally to ammonia and carbon dioxide.

By the action of a mixture of nitric and sulphuric acids upon guanidine nitrate, **nitro-guanidine**,  $\text{NH}_2\cdot\text{C}(\text{NH})\text{NH}\cdot\text{NO}_2$ , is obtained, which is readily reduced to **amino-guanidine**,  $\text{NH}_2\cdot\text{C}(\text{NH})\text{NH}\cdot\text{NH}_2$ . The latter, when boiled with alkalis or acids, breaks up into *hydrazine*,  $\text{N}_2\text{H}_4$ , ammonia, and carbon dioxide, and it yields with nitrous acid **diazo-guanidine**,  $\text{NH}_2\cdot\text{C}(\text{NH})\text{NHN}:\text{N}\cdot\text{OH}$ , which in its turn is decomposed by alkalis into water, cyanamide, and *hydrazoic acid*,  $\text{N}_3\text{H}$  (*Curtius*, *A.*, 1900, 314, 339).

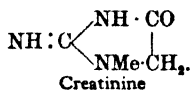
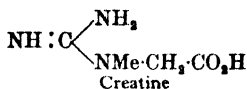
By the direct combination of cyanamide with glyccoll there is formed **glyccyamine**:



which readily loses water with formation of **glycoxyamidine**:



If, instead of glycocoll, its methyl derivative, sarcosine, is used, creatine and creatinine are formed (*Volhard*):



**Creatine** is present in the juice of muscle, and is prepared from extract of meat (*Liebig*). It crystallizes in neutral prisms (+H<sub>2</sub>O) of a bitter taste, is moderately soluble in hot water, but only slightly in alcohol. When heated with acids it loses water and yields **creatinine**, which is an invariable constituent of urine, and which forms a characteristic double salt with zinc chloride, 2C<sub>4</sub>H<sub>7</sub>N<sub>3</sub>O + ZnCl<sub>2</sub>. It is a strong base and much more readily soluble than creatine.

Creatinine is the methyl derivative of imino-hydantoin, and as such yields, when carefully hydrolysed, ammonia and methyl-hydantoin.

#### XIV. CARBOHYDRATES

Most of the commoner carbohydrates which occur in nature have been known for a long time. Cane-sugar was found in the sugar-beet by *Marggraf* in 1747, and dextrose in honey by *Glauber*. The transformation of starch into glucose (p. 349) was first observed by *Kirchoff* in 1811.

The name **carbohydrate** was formerly applied to certain substances which occur naturally in large quantities in the vegetable and animal kingdom, and which could be represented by the general formula C<sub>x</sub>(H<sub>2</sub>O)<sub>y</sub>, where  $x = 6$  or a multiple of 6, e.g. dextrose, C<sub>6</sub>(H<sub>2</sub>O)<sub>6</sub> or C<sub>6</sub>H<sub>12</sub>O<sub>6</sub>, cane-sugar, C<sub>12</sub>(H<sub>2</sub>O)<sub>11</sub> or C<sub>12</sub>H<sub>22</sub>O<sub>11</sub>, and starch [C<sub>6</sub>(H<sub>2</sub>O)<sub>5</sub>]<sub>x</sub>. In addition to these natural products, the group at the present time includes a number of compounds which have only been obtained synthetically, mainly as a result of the researches of *E. Fischer*. The number of carbon atoms in these varies con-

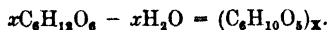
siderably. Carbohydrates are now known in which the hydrogen and oxygen are not present in the proportions of 2 atoms of hydrogen to 1 of oxygen, e.g. rhamnose  $C_6H_{12}O_5$ .

The carbohydrates are usually divided into the three following groups, according to their relative complexity:

**A. Monosaccharides.** Sometimes termed **Monoses**.—This is the simplest group of the carbohydrates, and the members are all polyhydroxy-aldehydes or ketones containing from 3–9 carbon atoms. The group includes the common substances arabinose,  $C_5H_{10}O_5$ , and the isomeric compounds,  $C_6H_{12}O_6$ , glucose or grape-sugar, and fructose or fruit-sugar. As a rule, the compounds are readily soluble in water, have a sweet taste, and do not crystallize very readily.

**B. Di-, Tri-, and Tetra-saccharides or Oligo-saccharides.**—These compounds may be regarded as anhydrides of the monosaccharides, usually derived by the elimination of 1 molecule of water from 2 mols. of the monosaccharide, of 2 mols. of water from 3 of monosaccharide or of 3 molecules of water from 4 of the mono-compound. It is not necessary that the 2 or 3 molecules of monose should be identical in structure, e.g. cane-sugar is the anhydride produced by the elimination of 1 mol. of water from 1 mol. of glucose and 1 of fructose. As anhydro-derivatives they are readily hydrolysed by mineral acids, yielding the monoses, from which they may be regarded as being derived. Most of the di- and tri-saccharides are soluble in water, crystallize very well, and also possess a sweet taste. Examples are cane-sugar, maltose, and milk-sugar.

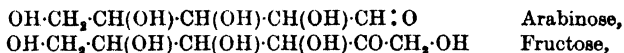
**C. Polysaccharides.**—This group includes the complex carbohydrates, such as starch, cellulose, &c. They may be regarded as derived from the monoses by the elimination of  $x$  mols. of water from  $x$  mols. of a monose, e.g.:



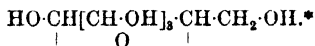
In conformity with such a structure, they are hydrolysed, but not very readily, yielding as the ultimate product a monosaccharide. The common ones, starch and cellulose, are insoluble in water, but tend to form colloidal solutions. They have no sweet taste, and have not been obtained in a crystalline form.

## A. Monosaccharides

These are all open-chain polyhydroxy-aldehydes or ketones,



and are divided into the two main groups **aldoses** and **ketoses**, according to their aldehydic or ketonic constitution. In aqueous solutions small amounts of the open-chain compound or their hydrates exist, but the compound exists mainly as a cyclic compound, in most cases an amylene oxide, e.g. an aldohexide:



As a rule, several hydroxyl groups are present in addition to

the aldehydic  $\begin{array}{c} \text{H} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{O} \end{array}$  or ketonic  $\begin{array}{c} \diagup \\ \text{C}:\text{O} \\ \diagdown \end{array}$  group, and invariably

one of these hydroxyl groups is in the  $\alpha$ -position with respect to the aldehydic or ketonic group.

The monosaccharides are usually divided into sub-groups, according to the number of **oxygen atoms** in the molecule, e.g.:

<b>Trioses,</b>	$\text{OH}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}:\text{O}$ and $\text{OH}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$ ;
<b>Tetroses,</b>	$\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_2\cdot\text{CH}:\text{O}$ ;
<b>Pentoses,</b>	$\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_3\cdot\text{CH}:\text{O}$ and $\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_4\cdot\text{CH}:\text{O}$ ;
<b>Hexoses,</b>	$\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_4\cdot\text{CH}:\text{O}$ and $\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_5\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$ ;
<b>Heptoses,</b>	$\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_5\cdot\text{CH}:\text{O}$ ;
<b>Octoses,</b>	$\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_6\cdot\text{CH}:\text{O}$ ;
<b>Nonoses,</b>	$\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_7\cdot\text{CH}:\text{O}$ .

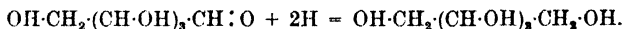
As a rule, the molecule of any single monose contains several asymmetric carbon atoms, e.g. a hexose,  $\text{OH}\cdot\text{CH}_2(\text{CH}\cdot\text{OH})_4\cdot\text{CH}:\text{O}$ , contains 4 asymmetric carbon atoms, and hence should exist in  $2^4$ , i.e. sixteen distinct optically active modifications, in addition to eight racemic forms. In most cases all the possible stereo-isomeric modifications are not known, but the number of such compounds known has been largely increased

\* For ring structure cf. Chap. LVI, A.

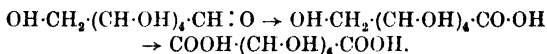
owing to the brilliant researches of *Emil Fischer* (B., 1890, 2114; 1894, 3189).

**General Characteristics of Aldoses.**—As aldehydes the aldoses possess most of the properties already described as characteristic of fatty aldehydes.

They are readily reduced by ordinary alkaline reducing agents, yielding polyhydric alcohols:

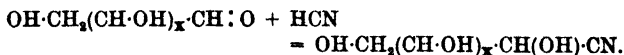


When oxidized, they yield first mono- and then dibasic acids, containing the same number of carbon atoms:



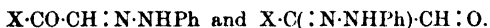
These reactions are of considerable importance as direct evidence of the aldehydic nature of the aldoses. The first stage of the oxidation is effected by mild oxidizing agents, such as chlorine, bromine water especially in presence of calcium benzoate, silver oxide, or ammoniacal solutions of cupric salts. The last-mentioned reaction is the basis of the usual volumetric method for the estimation of glucose and other aldoses. The aldose solution is added to a given volume of a standard *Fehling's* solution (a solution containing cupric sulphate, sodium ammonium tartrate, and caustic soda (p. 289)) until the blue colour just disappears on boiling. An even more exact method is to weigh the cuprous oxide (as such, as metallic copper, or as cupric oxide) formed by reducing a given volume of the sugar solution with an excess of *Fehling's* solution. The oxidation to a dibasic acid requires somewhat stronger oxidizing agents, e.g. nitric acid. With nitric acid in the absence of air a keto-monobasic acid can be formed, e.g. from glucose an acid  $\text{OH}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OH})_3\cdot\text{CO}\cdot\text{CO}_2\text{H}$ . *Kiliani* (B., 1922, 493).

Although the aldoses do not combine directly with ammonia or sodium hydrogen sulphite, they readily form additive compounds with hydrogen cyanide (cf. p. 342):



They react normally with hydroxylamine especially in alcoholic solution, yielding **oximes**, which can be converted into monoses containing a smaller number of oxygen atoms (p. 344).

They can also react normally with phenyl-hydrazine, yielding **phenyl-hydrazones**, which, as a rule, are sparingly soluble, colourless, crystalline compounds with definite melting-points. These are readily transformed back into the aldoses by treatment with hydrolysing agents or with benzaldehyde (A., 1895, 288, 140). Substituted phenyl-hydrazines, e.g. the *p*-bromophenyl- or diphenyl-hydrazine, are frequently used for isolating and characterizing sugars. One of the most characteristic properties of monoses is the formation of **osazones** or **diphenyl-hydrazones**. This reaction may be regarded as taking place in three distinct stages: (a) Formation of a phenyl-hydrazone,  $X\cdot CH(OH)\cdot CH:N\cdot NHPh$ , in the case of an aldose, and  $X\cdot C(:N\cdot NHPh)\cdot CH_2\cdot OH$  in the case of a ketose; (b) the oxidation of the  $>CH\cdot OH$  or  $\cdot CH_2\cdot OH$  group in the  $\alpha$ -position with regard to the carbon atom to which the hydrazino-group is attached and the formation of a  $>CO$  or  $\cdot CH:O$  group, e.g.:



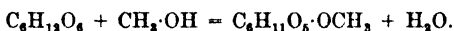
This oxidation occurs at the expense of the excess of phenyl-hydrazine, which becomes reduced to aniline and ammonia:



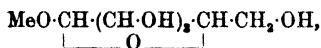
(c) The compounds thus obtained react with a further quantity of phenyl-hydrazine, so that a second hydrazino-group is introduced, e.g.  $X\cdot C(:N\cdot NHPh)\cdot CH:N\cdot NHPh$ , and an osazone formed (*E. Fischer*). From the above formulæ it is clear that the same osazone can be obtained from a ketose and an isomeric aldose (cf. Glucose and Fructose). These osazones are usually prepared by warming a dilute acetic acid solution of phenyl-hydrazine with the sugar for an hour or more on the water-bath. The products are yellow crystalline solids with definite melting-points; they are only sparingly soluble, and are largely made use of for characterizing the various monoses. Methyl-phenyl-hydrazine,  $NMePh\cdot NH_2$ , yields osazones with ketoses, but not with aldoses, and this difference is made use of in the separation of the two groups of compounds (B., 1902, 3141). The complex hydrazine di-methyl-hydrazino-diphenyl-methane,  $CH_2(C_6H_4\cdot NMe\cdot NH_2)_2$ , is often used in connexion with aldoses, as both  $NH_2$  groups react, giving crystalline compounds when two of the  $CH\cdot OH$  groups adjacent to the  $CHO$  group have the same spatial arrangement.

The hydroxylic nature of the aldoses can be established in various ways. Like all alcohols, they contain hydrogen atoms which can be replaced by metallic radicals. This replacement can be accomplished not only by means of metals themselves (cf. action of sodium on ethyl alcohol), but much more conveniently by means of the metallic hydroxides. The most common derivatives are the calcium, barium, or plumbous; thus from glucose,  $C_6H_{12}O_6$ , **calcium glucosate**,  $C_6H_{11}O_6 \cdot Ca \cdot OH$ , is readily obtained. Many of these metallic derivatives are sparingly soluble, and are therefore made use of in the isolation of certain sugars. They are readily transformed into the original sugar when decomposed by carbon dioxide in aqueous solution.

As alcohols the aldoses also give rise to ethers; the best known are the mono-methyl ethers of glucose, i.e. mixed ethers derived from the two alcohols, glucose and methyl alcohol:

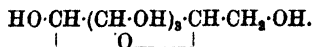


These compounds are usually spoken of as **glucosides** when derived from glucose or generally as **glycosides**, and are closely related to the natural glucosides, and exist in two stereo-isomeric forms  $\alpha$  and  $\beta$ , which have to be represented by cyclic structures:



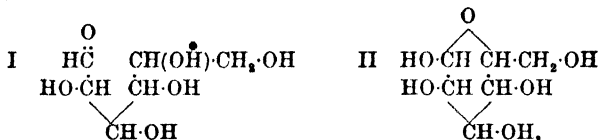
in which the  $\cdot CH(OMe) \cdot$  atom is a centre of dissymmetry and the  $\alpha$  and  $\beta$  forms are due to the spatial arrangement of the H and OMe attached to the atom. They are both optically active but not enantiomorphs as the spatial arrangement of the  $3CH \cdot OH$  groups is the same in both compounds. They may be obtained readily by the action of dry hydrogen chloride on a methyl alcoholic solution of glucose (*E. Fischer*, B., 1894, 1151). (See also Chap. LVI, A.)

Amylene oxide ring formulæ corresponding with the methyl glucosides have been given to the hexoses:



Carbon atom No. 1, i.e. in the terminal  $CH \cdot OH$ , becomes asymmetric and hence two stereo-isomerides are possible, corresponding with the  $\alpha$  and  $\beta$  forms of the methyl glucosides.

Comparing the acyclic I and the cyclic II structure for glucose:



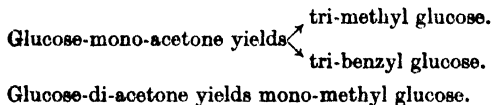
the difference is due to the labile  $\dot{\text{H}}$  migrating to the O of the  $\text{CH}:\text{O}$  group and a union between the carbons Nos. 1 and 5 by the oxygen attached to 1.

Completely methylated derivatives of the monosaccharides are obtained by taking the mono-methyl ethers and alkylating with methyl sulphate and sodium hydroxide. In this way **pentamethyl** derivatives,  $\text{C}_6\text{H}_7\text{O}(\text{OMe})_5$ , are obtained (*Haworth*, J. C. S., 1915, 8).

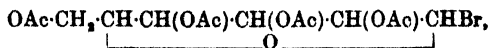
As alcohols they also form esters. Thus glucose when heated with acetic anhydride and anhydrous sodium acetate yields a pentacetate or **pentacetyl** derivative, which can be hydrolysed to acetic acid and glucose. The phosphoric esters are compounds of importance in biochemistry, e.g. in fermentation and in the chemistry of muscle.

They also form well-defined condensation products with acetone; cf. Chap. LVI, C.

Partially alkylated and acylated aldoses have been prepared; one of the common methods is to condense the aldose with acetone in the presence of a little hydrogen chloride (*Irvine and Macdonald, ibid.* 1915, 1706), then to alkylate or acylate, and finally to hydrolyse with mild hydrolytic reagents, so as to remove the acetone but to leave the alkyl or acyl groups intact (*Purdie and Young*, J. C. S., 1906, 1194; *Irvine and Scott, ibid.* 1913, 564, 575; *E. Fischer*, B., 1915, 266; 1916, 88). Thus:



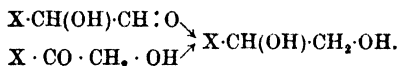
Important acyl derivatives are those of the type of **tetra-acetobromoglucose**:



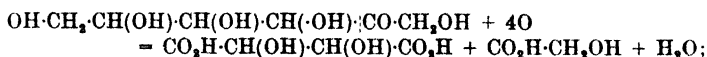


which contain a reactive bromine atom, and are hence of great value as synthetical reagents (cf. *Helpferich*, A., 1926-28, and Chap. LVI, F.). They are formed by the action of HBr (and HCl) in acetic acid solution on the pentacetyl glucose.

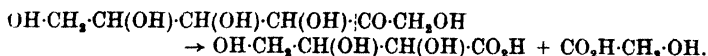
**General Characteristics of Ketoses.**—In the majority of their properties the ketoses resemble the aldoses, e.g. they react with hydroxylamine and phenyl-hydrazine in exactly the same manner. They form additive compounds with hydrogen cyanide, and are readily reduced to polyhydric alcohols. In certain cases the same alcohol is obtained by the reduction of a ketose and of an isomeric aldose, e.g. both *d*-glucose and *d*-fructose yield *d*-sorbitol on reduction:



The ketoses differ completely from the aldoses as regards their oxidation products. As ketones they do not yield mono- or dibasic acids containing the *same number of carbon atoms*,\* but always a mixture of simpler acids, e.g. *d*-fructose on oxidation with nitric acid yields a mixture of tartaric and glycollic acids:



or when boiled with mercuric oxide it yields glycollic and trihydroxy-butyric acids:



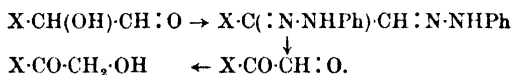
The ketoses also form metallic derivatives and acetyl derivatives.

**Alcoholic Fermentation of Monosaccharides.**—Many of the natural products, e.g. *d*-glucose and *d*-fructose, are readily fermented by yeast (*Saccharomyces*), yielding as chief products ethyl alcohol and carbon dioxide (p. 84). This decomposition is undoubtedly due to the presence of an enzyme, *Buchner's zymase*, which is contained in the cells of the organism. *Fischer's* researches have shown that all monoses cannot be

\* The formation of acids containing the same number of carbon atoms is theoretically possible, since two  $\cdot\text{CH}_2\cdot\text{OH}$  groups are present, but such acids have not been obtained.

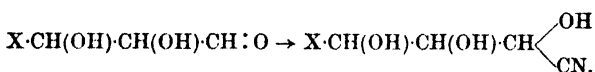
fermented, only certain of those containing 3 or a multiple of 3 carbon atoms. Even such monoses are not all readily fermented, e.g. *d*-glucose is fermented more readily than *l*-glucose, and the isomeric guloses cannot be fermented by yeast. There appears to be an intimate relationship between the configuration of the monose molecule and of the ferment (enzyme) which is capable of decomposing it. *Fischer* has compared this relationship to that of a lock and its corresponding key, and *Armstrong* to a human hand and the corresponding glove.

**Conversion of an Aldose into an Isomeric Ketose.**—This is an interesting transformation due to *E. Fischer*, and consists in converting the aldose into its osazone, which on hydrolysis with hydrochloric acid yields phenyl-hydrazine and a poly-hydroxy-ketonic aldehyde, usually known as an **osone**. When the osone is reduced, the aldehydo-group is converted into a primary alcoholic radical, and a hydroxy-ketone (ketose) isomeric with the original aldose is obtained, e.g.:

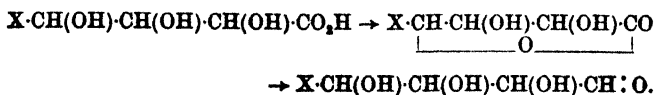


By this means *d*-glucose can be transformed into *d*-fructose.

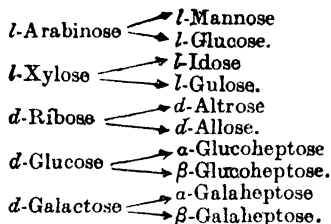
**Synthesis of a Monosaccharide from a Simpler Monosaccharide.**—The aldose is converted into its cyanhydrin by means of hydrogen cyanide (*Kiliani*):



As this reaction involves the introduction of a further asymmetric carbon atom into the molecule, two distinct optically active nitriles will be formed. As the two compounds are not related to one another as object to mirror image, they will not be optical antipodes, and will not necessarily be formed in equal amount. The mixture of cyanides is hydrolysed, the resulting hydroxy acids converted into **lactones** and then reduced with sodium amalgam, when a mixture of two sugars is obtained:

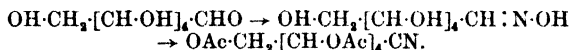


Examples are:

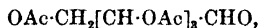


By similar methods *E. Fischer* has succeeded in preparing **octoses** and **nonoses**. For configuration of the latter see *Pierce*, *J. Biol. C.*, 1915, **23**, 327. Two heptoses have been isolated from natural products, viz. a **mannoketoheptose**, from Avogadro pear (*Abs.*, 1917, **i**, 118), and **sedoheptose**, from the leaves and stems of *Sedum spectabile*.

**Conversion of a Monosaccharide into a Simpler Monosaccharide** (*Wohl*, *B.*, 1893, 730).—1. The aldose is converted into its oxime, which reacts with acetic anhydride, yielding an acetylated hydroxy-nitrile, e.g.:

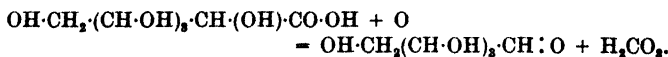


The nitrile when treated with ammoniacal silver nitrate solution loses hydrogen cyanide and yields the acetyl derivative of a lower monose, e.g.:



from which the monose itself is readily obtained.

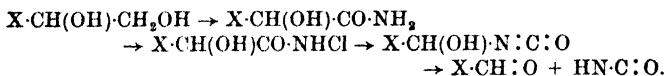
2. Another method worked out by *Ruff* (*B.*, 1898, 1573; 1900, 1798; 1902, 2360) consists in oxidizing the aldose to the corresponding monobasic acid, and then oxidizing the calcium salt of this with ferric acetate and hydrogen peroxide. Carbonic acid is split off and an aldose obtained:



The aldose can be isolated as its phenylhydrazone, and this with benzaldehyde yields the free aldose.

3. A third method consists in oxidizing to the lactone of the monobasic acid, preparing the amide of the acid by the

addition of ammonia to the lactone and the action of hypochlorous on the amide (*Hofmann* reaction, p. 211):



In this way *d*-glucose yields *d*-arabinose and *d*-galactose *d*-lyxose (*Warman*, Abs., 1915, i, 387; 1917, i, 546).

**Trioses.**—When glycerol is oxidized with dilute nitric acid or other oxidizing agents, a product  $\text{C}_3\text{H}_6\text{O}_3$  is obtained, which has been termed **glycerose**. This has been shown to consist of the ketone, dihydroxyacetone,  $\text{OH}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$ , with a small amount of the isomeric aldehyde, glyceraldehyde,  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}:\text{O}$ ,\* and may be regarded as the simplest monosaccharide. It is a syrup, possesses most of the characteristic properties of the simpler sugars, and when warmed with alkalis undergoes condensation and yields a hexose ( $\alpha$ -acrose) (p. 354) which closely resembles fructose.

**Tetroses**,  $\text{C}_4\text{H}_8\text{O}_4$ .—A tetrose, **erythrose**, can be obtained by the oxidation of erythritol,  $\text{OH}\cdot\text{CH}_2[\text{CH}\cdot\text{OH}]_2\cdot\text{CH}_2\cdot\text{OH}$ , with nitric acid, and is probably a mixture of an aldose and ketose. Other tetroses can be obtained from the pentoses by the general methods described on p. 344.

**Pentoses.**—The pentoses are characterized by the fact that they yield furfuraldehyde or methyl-furfuraldehyde upon prolonged boiling with hydrochloric acid, water being eliminated. This reaction is largely made use of for their quantitative estimation (B., 1892, 2912; 1898, 2570). Arabinose gives furfuraldehyde itself, while its homologue, rhamnose, gives methyl-furfuraldehyde. When warmed with hydrochloric acid and phloroglucinol, cherry-red colorations are produced. The pentoses do not appear to exist free in the animal or vegetable kingdom, but are readily formed by the hydrolysis of various natural gummy carbohydrates.

***l*-Arabinose**,  $\text{C}_5\text{H}_{10}\text{O}_5$ ,  $= \text{OH}\cdot\text{CH}_2\cdot[\text{CH}\cdot\text{OH}]_3\cdot\text{CH}:\text{O}$ , is produced by boiling gum-arabic, cherry gum, or beet-root chips with dilute sulphuric acid, and forms prisms which dissolve in water to a dextro-rotatory solution. It combines with hydrogen cyanide, and thus yields the nitriles of two stereoisomeric hydroxy-caproic acids, viz. *l*-mannonic acid (*Kiliani*)

\* For preparation of glyceraldehyde cf. J. A. C. S., 1914, 2223.

and *l*-gluconic acid (*E. Fischer*). In addition to *l*-arabinose, a *d*-arabinose and a *d*-*l*- or racemic arabinose are also known. They are related to one another in exactly the same manner as *l*-, *d*-, and *r*-tartaric acid. The corresponding alcohol is arabitol.

***l*-Xylose**, or *Wood-sugar*, is stereo-isomeric with arabinose, and is prepared by boiling wood-gum, straw, and jute with dilute sulphuric acid, and is very similar to arabinose. (For its constitution see B., 1891, 537.) The corresponding alcohol is xylitol. **Ribose** (B., 1891, 4214) and **Lyxose** (B., 1899, 1798; J. C. S., 1928, 1221) are stereo-isomeric with arabinose.

**Rhamnose**, or *Isodulcitol*,  $C_6H_{12}O_5$ ,  $= CH_3 \cdot [CH \cdot OH]_4 \cdot CH : O$ , is obtained from several glycosides, e.g. quercitrin or xanthorhamnin (yellow needles, present in French berries, *Rhamnus tinctoria*, &c.), by the action of dilute sulphuric acid. It forms colourless crystals which contain  $1H_2O$ , melts at  $93^\circ$ , and distilled with sulphuric acid yields  $\alpha$ -methyl-furfuraldehyde.

Several isomerides of rhamnose are known, e.g. **fucose** from sea-weed, **epifucose**, **quinovose**, **rhodose** and **isorhamnose**.

**Hexoses**.—The hexoses constitute the most important group, as they contain all the more common natural monosaccharides, e.g. *d*-glucose, *d*-fructose, *d*-galactose, &c. These occur in the free state in the juices of ripe fruits, and are also found combined with acids and other compounds in the ether- or ester-like compounds known as glycosides. They are also formed by the hydrolysis of more complex carbohydrates, e.g. cane-sugar, maltose, milk-sugar, or starch, either under the influence of mineral acids or of enzymes. They are sweet, and for the most part crystalline compounds readily soluble in water, sparingly in absolute alcohol, and insoluble in ether. They possess the chemical properties of pentahydroxy-aldehydes and ketones.

**Aldohexoses**.—The common aldohexoses have the constitution represented by the formula:



In this formula the 4 carbon atoms contained within the brackets are asymmetric carbon atoms, and hence such a compound should exist theoretically in  $2^4$ , i.e. 16 stereo-isomeric active forms in addition to 8 racemic forms, and all of these have been prepared.

Aldohexose.	Monobasic Acid.	Dibasic Acid $\text{CO}_2\text{H}[\text{CH}(\text{OH})]_4\text{CO}_2\text{H}$ .
<i>d</i> - & <i>l</i> -Mannose	<i>d</i> - & <i>l</i> -Mannonic acid	<i>d</i> - & <i>l</i> -Mannosaccharic
<i>d</i> - & <i>l</i> -Glucose	<i>d</i> - & <i>l</i> -Gluconic acid	<i>d</i> - & <i>l</i> -Saccharic
<i>d</i> - & <i>l</i> -Gulose	<i>d</i> - & <i>l</i> -Gulonic acid	<i>d</i> - & <i>l</i> -Saccharic
<i>d</i> - & <i>l</i> -Idose	<i>d</i> - & <i>l</i> -Idonic acid	<i>d</i> - & <i>l</i> -Idosaccharic
<i>d</i> - & <i>l</i> -Galactose	<i>d</i> - & <i>l</i> -Galactonic acid	<i>i</i> -Mucic
<i>d</i> - & <i>l</i> -Talose	<i>d</i> -Talonic acid	<i>d</i> -Talomucic
<i>d</i> - & <i>l</i> -Altrose	<i>d</i> -Altronic acid	<i>d</i> -Talomucic
<i>d</i> - & <i>l</i> -Allose	<i>d</i> -Allonic acid	Allomucic
	Alcohol.	M.-pt. of Osazone.
	<i>d</i> - & <i>l</i> -Mannitol	206°
	<i>d</i> - & <i>l</i> -Sorbitol	Ibid.
	<i>d</i> - & <i>l</i> -Sorbitol	156°
	<i>d</i> - & <i>l</i> -Iditol	156°
	<i>i</i> -Dulcitol	206°
	<i>d</i> -Talitol	188°
	—	183°–185°
	—	183°–185°

Of these only 4 occur naturally.

All of these hexoses have to be represented by the same structural formula, and only differ as regards the spatial arrangements of the various radicals within the molecule. All are optically active in solution, and the majority form pairs of optical antipodes, e.g. *d*- and *l*-glucose, which are related in exactly the same manner as *d*- and *l*-tartaric acids. The members of such a pair are identical as regards their ordinary chemical and physical properties, with the exception of their effects on polarized light, and their behaviour towards enzymes or ferments generally. As a rule, one of the two compounds exists naturally, e.g. *d*-glucose, and the second must be prepared by artificial means. The two are able to form a racemic compound, which differs as regards its physical properties from the active components.

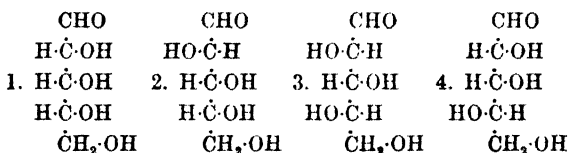
The determination of the configuration of each aldohexose has been accomplished by *E. Fischer* largely from a study of the following points: (a) The relationship of the aldohexose to the aldopentoses, e.g. *l*-arabinose can be transformed into a mixture of *l*-glucose and *l*-mannose, and hence in all three compounds the configuration of the following part of the molecule —  $\text{OH}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})$  — must be identical. (b) The nature of the dibasic acid formed on oxidation, or of the alcohol formed on reduction. When reduced *d*-galactose

yields an inactive hexahydric alcohol, viz. *i*-dulcitol, and from this it follows that in the *d*-galactose molecule the H and OH radicals must be so spatially arranged that when the  $\cdot\text{CH}:\text{O}$  group is converted into a  $\text{CH}_2\cdot\text{OH}$  group a symmetrical molecule is obtained (see formula below). (c) The nature of the osazone; e.g. *d*-glucose and *d*-mannose both give rise to the same osazone—*d*-glucosazone—and hence the spatial arrangements of the two molecules must be identical, with the exception of the part  $\cdot\text{CH}(\text{OH})\cdot\text{CH}:\text{O}$ .

As the result of such methods, the configurations given on p. 349 have been arrived at for some of the commoner aldohexoses (B., 1891, 2683; 1894, 3211).

The actual positions of H and OH are often determined by conversion into *d*- or *l*-tartaric acid (p. 287). Thus *d*-glucose  $\rightarrow$  *d*-saccharic acid  $\rightarrow$  *d*-tartaric acid, establishes the positions of the OH and H groups attached to C atoms 2 and 3, but *d*-saccharamide with bromine and alkali gives *l*-tartaric acid, and thus the position of H and OH groups attached to C atoms 3 and 4 (formula p. 349) (Bergmann, B., 1921, 2651).

A clearer conception of the manner in which such arguments are used can be gathered by a study of the aldopentoses. Eight active forms are theoretically possible, and the *d*- and *l*-forms of arabinose, xylose, lyxose, and ribose are the compounds actually known. The possible configurations are the four given below and their enantiomorphs:

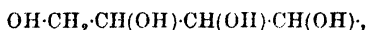


Since arabinose and ribose give the same osazone they must be either 1 and 2 or 3 and 4. Arabinose on oxidation gives an optically active trihydroxyglutaric acid, hence arabinose can only have the configuration 2 or 4. Further, arabinose with hydrogen cyanide and subsequent hydrolysis and oxidation gives two *active* dicarboxylic acids, and must therefore have the structure 2, as one of the acids derived in this way from 4 would be optically inactive by internal compensation. If 2 represents *d*-arabinose, then its enantiomorph represents

*l*-arabinose. As No. 2 represents *d*-arabinose, No. 1 must represent *d*-ribose.

As xylose yields an inactive trihydroxyglutaric acid when oxidized, it must be represented by configuration No. 3, and hence lyxose is No. 4.

Since *d*-arabinose when treated with hydrogen cyanide and the product hydrolysed and reduced yields a mixture of *g*-glucose and *d*-mannose, it follows that in these two latter the spatial arrangements in the portion,



must be identical, as shown in the constitutional formulæ given below:

1.	CHO	CHO	CHO	CHO
2.	HO·Ċ·H	H·Ċ·OH	H·Ċ·OH	H·Ċ·OH
3.	HO·Ċ·H	H·Ċ·OH	HO·Ċ·H	HO·Ċ·H
4.	H·Ċ·OH	HO·Ċ·H	H·Ċ·OH	HO·Ċ·H
5.	H·Ċ·OH	HO·Ċ·H	H·Ċ·OH	H·Ċ·OH
6.	ĊH <sub>2</sub> ·OH	ĊH <sub>2</sub> ·OH	ĊH <sub>2</sub> O	ĊH <sub>2</sub> ·OH
	<i>d</i> -Mannose	<i>l</i> -Mannose	<i>d</i> -Glucose	<i>d</i> -Galactose

For other methods of representing the monosaccharide configuration see Chap. LVI, A.

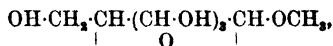
*d*-Glucose, *Grape-sugar* or *dextrose*,  $\text{C}_6\text{H}_{12}\text{O}_6 + \text{H}_2\text{O}$ , occurs together with *d*-fructose in most sweet fruits, in honey, also diabetic urine. It is prepared by the hydrolysis of more complex carbohydrates, e.g. sucrose or starch. The usual method, the hydrolysis of starch with dilute sulphuric acid in England or hydrochloric acid in U.S.A., yields a commercial product which contains, in addition to dextrose, dextrine and unfermentable substances. The conditions are 0.5 per cent commercial sulphuric acid, temperature  $110^\circ$ – $125^\circ$  and pressure 10–30 lb.; subsequent neutralization with calcium carbonate, filtration, decolorization with animal charcoal and evaporation under reduced pressure. Solutions of glucose obtained by above process or by action of hydrochloric acid on wood cellulose are used for the manufacture of power alcohol by fermentation.

It crystallizes from water in nodular masses made up of six-sided plates which melt at  $86^\circ$ , and from methyl alcohol in small anhydrous prisms free from water; m.-pt.  $146^\circ$ . It is dextro-rotatory,  $[\alpha]_D = 52.6^\circ$ , hence the name "*dextrose*".



A freshly-prepared solution turns the plane of polarization almost twice as much as one which has been kept or heated to boiling, a phenomenon which is known as "bi-, multi-, or muta-rotation". This is due to the formation of an equilibrium mixture of two stereo-isomeric cyclic *d*-glucoses in the solution, corresponding with the  $\alpha$ - and  $\beta$ -methyl-*d*-glucosides in structure (cf. p. 340 and Chap. LXXI, 12). The strength of a solution of glucose is usually determined polarimetrically from its specific rotatory power, or gravimetrically by determining the weight of cuprous oxide obtained by the reduction of *Fehling's* solution with a given volume of the solution (cf. p. 338).

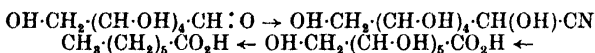
*d*-Glucose-phenyl-hydrazone,  $C_{12}H_{18}O_5N_2$ , forms fine crystals which melt at  $115^\circ$ . Another modification melts at  $144^\circ$ . *d*-Phenyl-glucosazone crystallizes in sparingly soluble needles. The rotation produced by the hydrazones and osazones may be the opposite of that of the mother substance. It is an important point for the recognition of the latter. *d*-Pentacetyl-glucose,  $C_6H_7O(OC_2H_3O)_5$ , melts at  $111^\circ$ . *d*-Glucosone,  $CH_2(OH)\cdot[CH(OH)]_3\cdot CO\cdot CHO$ , forms a syrup which does not ferment with beer yeast, and which yields the osazone immediately with phenyl-hydrazine. **Methyl-glucoside**,



exists in a pair of stereo-isomeric modifications, the  $\alpha$  compound melts at  $165^\circ$  and the  $\beta$  at  $107^\circ$ . *l*-Glucose resembles *d*-glucose closely, excepting that it turns the plane of polarization as strongly to the left as the latter does to the right. *dl*-Glucose, from *i*-gluconic acid, is a colourless syrup. The osazone, *dl*-glucosazone, melts at  $216^\circ$ , and, apart from rotatory power, is deceptively like the *d*- and *l*-osazones.

**Constitution of *d*-Glucose.**—Its constitution as a pentahydroxy aldehyde follows from the formation of a pentacetyl derivative, and from its oxidation first to a monobasic acid (gluconic acid) and then to a dibasic acid (saccharic acid), both of which contain the same number of carbon atoms as glucose. A proof both of its aldehydic nature and of the normal chain structure was afforded by *Kiliani* (B., 1886, 19, 767), who prepared the cyanhydrin, hydrolysed this to the hexa-hydroxy-carboxylic acid, and, by reducing this

with hydriodic acid and phosphorus, obtained *n*-heptylic acid:



a product which could not have been formed if the glucose had possessed either a ketonic structure or an iso-chain (cf. Fructose). Cf. Chap. LVI, A., for ring structure.

***d*-Mannose** is stereo-isomeric with *d*-glucose, and is formed together with *d*-fructose by the cautious oxidation of mannitol, also by boiling the reserve cellulose of the seed of the Brazil-nut (*Bertholletia excelsa*), or of the seeds of the Ivory-palm (*Phytelephas macrocarpa*), with dilute mineral acid, and by reducing mannonic acid lactone with sodium amalgam. It forms colourless crystals readily soluble in water, is dextro-rotatory  $[\alpha]_D = +14.36^\circ$ , and yields the same osazone as *d*-glucose. When treated with sodium amalgam it passes readily into *d*-mannitol. The **hydrazone** melts at  $195^\circ$ , and is sparingly soluble in water. ***dl*-Mannose** forms a colourless syrup. The osazone is identical with that from *dl*-fructose. ***l*-Mannose** is not so readily fermented as the *d*-isomeride.

***d*-Galactose** is formed together with *d*-glucose by the hydrolysis of milk-sugar with dilute acid, and also from certain gums. It crystallizes in slender needles, and melts at  $166^\circ$ , is dextro-rotatory,  $[\alpha]_D = +80.3^\circ$ , and readily fermented. Its **pentacetyl** derivative melts at  $143^\circ$  (for four isomeric forms cf. Hudson, J. A. C. S., 1915, 1589; 1916, 1223),  **$\alpha$ -methyl-galactoside** at  $111^\circ$ , and the stereo-isomeric  **$\beta$ -compound** at  $173^\circ$ – $175^\circ$ .

**Talose** is a syrup. The phenyl-hydrazone is very readily soluble in water (difference from galactose).

**Ketohexoses**,  $\text{OH}\cdot\text{CH}_2\cdot[\text{CH}\cdot\text{OH}]_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$ , are structurally isomeric with the aldohexoses. As ketones they cannot be oxidized to acids containing the same number of carbon atoms (cf. p. 342). Although ketones, they can reduce alkaline copper solutions. The formula contains 3 asymmetric carbon atoms, and hence eight active stereo-isomerides are possible, of which six are actually known.

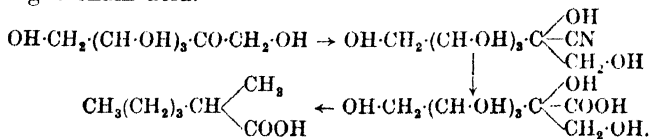
***d*-Fructose**, *Fruit-sugar* or *levulose*,  $\text{C}_6\text{H}_{12}\text{O}_6$ , is almost invariably found along with *d*-glucose in the juice of sweet fruits and also, together with the latter, in honey. It is formed along with *d*-glucose by the inversion of cane-sugar, and together with *d*-mannose by the cautious oxidation of *d*-mannitol;

also from *d*-phenyl-glucosazone, and therefore indirectly from *d*-glucose. It is most easily prepared by heating inulin (p. 372) with very dilute acid; is somewhat difficult to obtain crystalline, and then forms hard, anhydrous, rhombic crystals melting at 95°. It is lævo-rotatory, although belonging genetically to the *d*-series, and has  $[\alpha]_D^{20} = -92^\circ$ . It may be separated from *d*-glucose by means of its sparingly soluble lime compound.

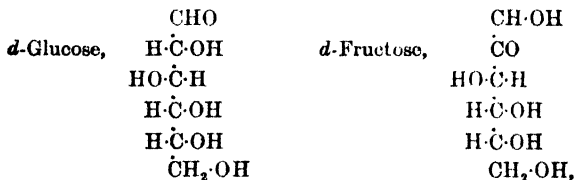
Its close relationship to *d*-glucose is shown by the fact that it yields the same osazone, and on reduction yields a mixture of *d*-mannitol and *d*-sorbitol. On oxidation it yields glycollic and tartaric acids, or glycollic and trihydroxy-butyric acids (cf. p. 342). With methyl-phenyl-hydrazine it yields a colourless osazone. It is fermentable, but not so readily as *d*-glucose. It is manufactured from inulin for the use of diabetic patients in the place of cane-sugar.

*l*-Fructose closely resembles *d*-fructose, but is dextro-rotatory, and as it is not readily fermented, can easily be obtained from *dl*-fructose, which is a syrup.

**Constitution of *d*-Fructose.**—The formation of acids with a smaller number of carbon atoms points to its ketonic structure, and this was further proved by *Kiliani*, who hydrolysed the cyanhydrin, and then reduced the hydroxy acid thus obtained with hydriodic acid and phosphorus, and obtained methyl-butyl-acetic acid, i.e. a branched and not a straight chain acid.



Its configuration as *hexanepentol-2-one* — + + follows from its close relationship to *d*-glucose.

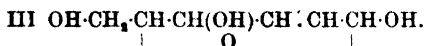
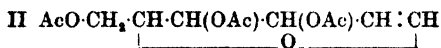
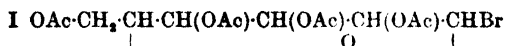


since both yield the same osazone. For cyclic structure see Chap. LVI, A.

Other stereo-isomeric ketohexoses are *d*-tagatose, obtained by the action of potassium hydroxide solution on *d*-galactose. It melts at 124°, and yields the same osazone as *d*-galactose. *d*-Sorbose, obtained by oxidizing *d*-sorbitol; and *l*-sorbose, obtained as a by-product in the preparation of *d*-tagatose. *l*-Sorbose is required for the manufacture of the vitamine *l*-ascorbic acid (Chap. LVI, E.), and is made by the action of the bacillus, *B. xylinum*, on *d*-sorbitol obtained by the catalytic hydrogenation of *d*-glucose. The fructoses correspond in configuration with the arabinoses, tagatose with lyxose, and the sorboses with the xyloses.

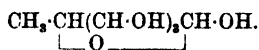
**Resolution of Racemic Sugars.**—One method is by means of *d*-phenylamyl-hydrazine,  $C_6H_5N(C_5H_{11})\cdot NH_2$ , separating the two phenylamyl-hydrazones by fractional crystallization and regenerating the active sugars by hydrolysis (*Neuberg*, B., 1905, 868). Another method consists in combining the aldose with an active mercaptan, e.g. *d*-amylmercaptan. *d*-*l*-Arabinose reacts with *d*-amylmercaptan, giving a mixture of two isomerides, viz. *d*-arabinose-*d*-amylmercaptal and *l*-arabinose-*d*-amylmercaptal,  $OH\cdot CH_2(CH\cdot OH)_3\cdot CH(SC_5H_{11})_2$ , which can be separated by fractional crystallization from alcohol, in which the former is less soluble (*Abs.*, 1916, i, 308).

**Unsaturated Monosaccharides.**—Glucal,  $C_6H_{10}O_4$ , is a syrup obtained by the following series of reactions: Acetobromoglucose I reduced with zinc and acetic acid gives triacetylglucal II, the pyranose structure of which has been confirmed by *Hirst* and *Woolvin* (J. C. S., 1931, 1131). On hydrolysis with boiling barium hydroxide solution the product is isoglucal III, B., 1931, 158.



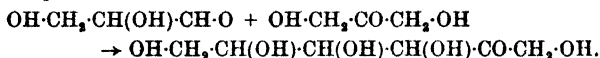
When reduced dihydroglucal,  $C_6H_{12}O_4$ , m.-pt. 86°, is obtained, and this does not show unsaturated or reducing properties (*E. Fischer*, B., 1914, 196). Glucal has been isolated from the hydrolytic products of nucleic acid (*Z. physiol.*, 1917, 100, 241). Other glucals are known (B., 1928, 1825), and are of value for synthetic purposes. Thus glucal readily yields

$\alpha$ -methylmannoside by the action of perbenzoic acid (p. 516). With cold dilute sulphuric acid glucose yields **deoxyglucose**,



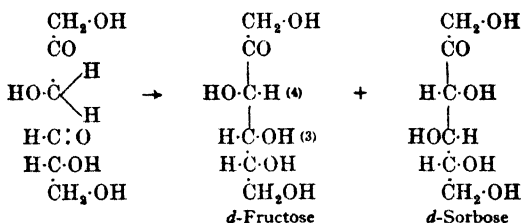
Many homologues of deoxyglucose occur naturally, e.g. deoxy-*d*-ribose.

**Synthesis of Hexoses.**—Four methods have been used for synthesizing hexoses. 1. The polymerization of formaldehyde by means of lime water (*O. Loew*, 1886). The product was termed **formose**, but has since been shown to be a mixture of hexoses containing  $\alpha$ -acrose. 2. By the addition of bromine to acrolein and the decomposition of the dibromide with barium hydroxide (*E. Fischer* and *Tafel*). Glyceraldehyde (Chap. IX, C.) is first formed, and this may then undergo the aldol condensation. 3. By the action of barium hydroxide on glycerose (p. 345), and hence a synthesis from glycerine. Two isomeric hexoses were isolated, viz.  $\alpha$ - and  $\beta$ -acroses (*E. Fischer* and *Tafel*, B., 1887, 1093, 3384; 1889, 97). The synthesis consists in an aldol condensation of the two components of glycerose, viz. glyceraldehyde and dihydroxy-acetone:



Pure glyceraldehyde also yields the two hexoses under similar conditions, due to the conversion of part of the aldehyde into dihydroxyacetone. 4. By the action of alkalis on glycolaldehyde,  $\text{OH·CH}_2\text{·CHO}$  (p. 236; *Jackson*, J. C. S., 1900, 129), a tetrose,  $\text{C}_4\text{H}_8\text{O}_4$ , and  $\alpha$ - and  $\beta$ -acroses are formed and are separated by means of their osazones. The  $\alpha$ -acrose obtained by these reactions has been the starting-point for the syntheses of most of the other hexoses. The  $\alpha$ -acrose is converted into its osazone; this is hydrolysed to the osone, and then reduced to the ketose, when *dl*-fructose is obtained. The osazone obtained from  $\alpha$ -acrose is identical with *dl*-glucosazone, but as the same osazone is formed from glucose, mannose, and fructose, the identity of the original  $\alpha$ -acrose is not established. According to *Neuberg* (B., 1902, 2626) and *Schmitz* (B., 1913, 2327),  $\alpha$ -acrose is in reality *dl*-fructose, as it has been obtained crystalline, m.-pt.  $129^\circ$ – $130^\circ$ , and has been found to react with methylphenylhydrazine, which

does not form osazones with aldoses. Similarly it has been shown that  $\beta$ -acrose is *dl*-sorbitose. Thus the primary products are both ketoses formed by the condensation of glyceraldehyde with dihydroxyacetone. Fischer and Baer (Helv., 1936, 519) show that 0.01 N barium hydroxide reacts with *d*-glyceraldehyde yielding dihydroxyacetone, which then condenses with the *d*-aldehyde yielding a mixture of equal amounts of *d*-fructose and *d*-sorbitose. No racemization of the aldehyde occurs before condensation. The isomeric ketoses *d*-psicose and *d*-vagatose are not formed and evidently there is a preferential formation of products in which the OH groups attached to C atom 3 and 4 have opposite configurations.



The scheme (p. 357) gives a *résumé* of the steps involved in the synthesis of the other hexoses from  $\alpha$ -acrose. Stoklasa (C. R., 1913, 156, 646) has shown that radium emanation causes hydrogen to reduce carbon dioxide to formaldehyde in the presence of  $\text{KHCO}_3$ , and that the aldehyde then polymerizes to a mixture of reducing sugars.

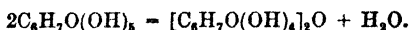
The hexoses are reactive to alkalis and any one of the hexoses, glucose, mannose, fructose with dilute alkali gives an equilibrium mixture (cf. Chap. LVI, A.).

## B. Di-, Tri-, and Tetra-saccharides: Oligosaccharides

This group comprises those carbohydrates which may be regarded as derived from 2, 3 or 4 molecules of a monosaccharide by the elimination of 1, 2 or 3 mols. of water respectively. As such anhydrides, they are all readily hydrolysed when boiled with dilute acids, yielding monoses, usually hexoses. Thus cane-sugar yields a mixture of *d*-glucose and

*d*-fructose; maltose yields *d*-glucose only; milk-sugar yields *d*-glucose and *d*-galactose:  $C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6$ .

Raffinose or melitriose is a type of a trisaccharide, and on hydrolysis yields melibiose and *d*-fructose. The hydrolysis in most of these cases can not only be effected by means of acids but also by means of sucroclastic enzymes, e.g. diastase and invertase hydrolyse cane-sugar, maltase malt-sugar, &c. The readiness with which the disaccharides are hydrolysed indicates a union of the 2 molecules of monosaccharide by means of oxygen and not of carbon. The disaccharides are thus ethereal anhydrides of the hexoses, e.g. cane-sugar is *d*-glucose-*d*-fructose anhydride, and malt-sugar *d*-glucose anhydride, &c. In this anhydride formation 8 of the original 10 OH groups have remained intact, as the disaccharides readily yield **octa-methyl** and **octacetyl** derivatives and **octa-nitrates** (J. A. C. S., 1919, 235):

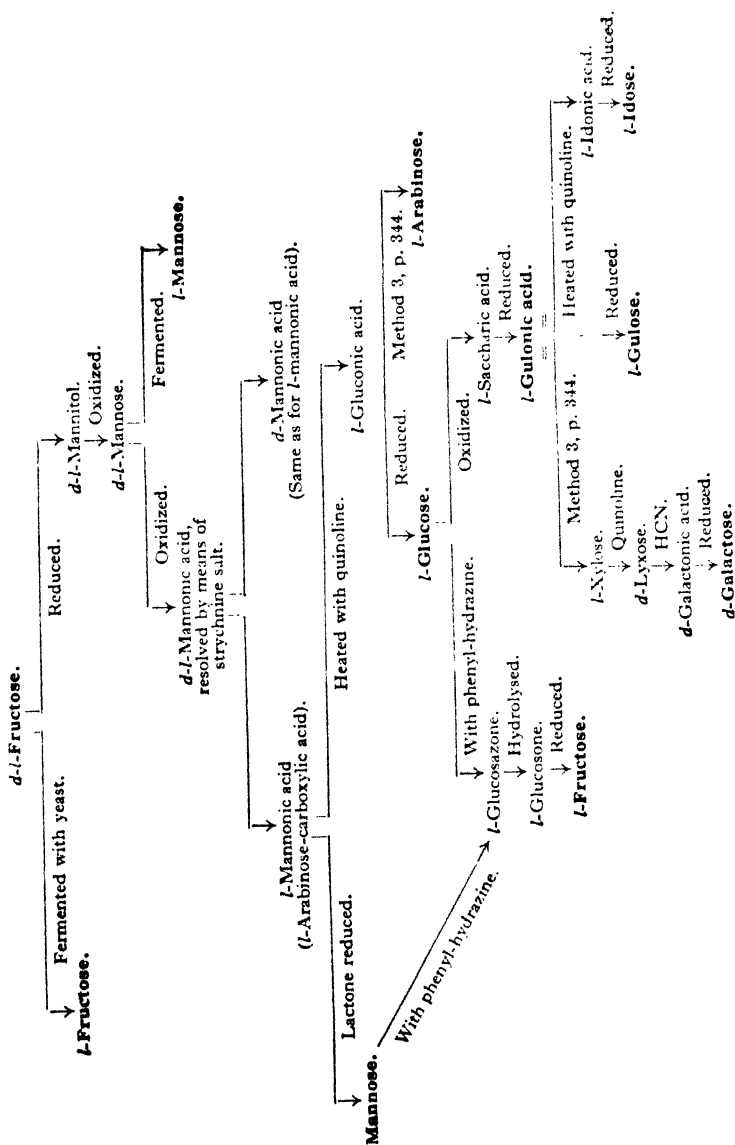


As a rule, 2 stereo-isomeric octa-acetyl derivatives are obtained from each disaccharide (*Hudson and Johnson, ibid.* 1915, 1270, 1276), and these are related in much the same manner as  $\alpha$ - or  $\beta$ -methyl glucosides (Chap. LVI, F.).

As milk-sugar and malt-sugar both reduce *Fehling's* solution, it is highly probable that they still retain a CHO group of one of the component monose molecules. And as cane-sugar is not a reducing sugar, it probably contains no carbonyl group. The chief difficulty in assigning structural formulæ to the disaccharides is to determine the oxygen atoms which take part in the anhydride formation, and to determine with certainty which of the 4 stereo-isomeric forms of a particular monosaccharide (e.g.  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$  glucose) has taken part in the anhydride formation. For details see Chap. LVI, B., and LXIX, D.

The compounds possess for the most part a sweet taste, and crystallize more readily and are more stable than the monosaccharides, but resemble the latter in solubility. They are not directly fermentable, but can be fermented after hydrolysis to monosaccharides. All those which occur naturally are optically active.

**Cane-sugar** or **Sucrose**, *Saccharobiose*,  $C_{12}H_{22}O_{11}$ , occurs in red beet (Beta) 16-20 per cent, in the sugar-cane (*Saccharum*) 14-26 per cent in the juice, in the sugar-maple (*Sorghum*),





together with invert sugar in the mahua flower (*Bassia latifolia*), and in many other plants, chiefly in the stem.

*Preparation.*—(a) From sugar-cane by expressing the juice and evaporating it until crystallization begins. (b) From sugar-beet by a systematic extraction of the pulp with water, e.g. by the "diffusion process". The impure juice is then treated with lime ("defecation"), the excess of the latter thrown down by carbon dioxide ("saturation"), and the syrup filtered through animal charcoal, and evaporated *in vacuo* to crystallization. From the mother-liquid of molasses the crystallizable sugar still present can be obtained as the sparingly soluble strontium saccharate,  $C_{12}H_{22}O_{11} \cdot SrO$ , which is then suspended in water and decomposed by carbon dioxide ("desugarizing of molasses"). The molasses are frequently used as a source of power alcohol (pp. 88 and 349).

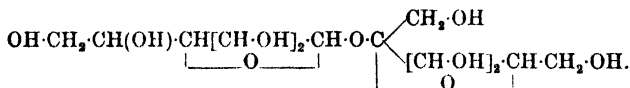
Cane-sugar crystallizes in large monoclinic prisms, as is well seen in sugar-candy, and is soluble in one-third of its weight of water. It is not turned brown when heated with potash, and yields saccharates with lime and strontia, e.g.  $C_{12}H_{22}O_{11} + CaO + 2H_2O$ ;  $C_{12}H_{22}O_{11} + 2CaO$ ;  $C_{12}H_{22}O_{11} + 3CaO$ . Concentrated sulphuric acid produces charring (difference from *d*-glucose). Cane-sugar melts at  $160^\circ$ , and remains in the amorphous condition for some time after cooling (barley-sugar); when heated more strongly, it becomes brown from the formation of caramel or sugar-dye, and finally chars.

The percentage of sugar in a solution of unknown strength can be determined from the specific rotatory power ( $[\alpha]_D^{20} = +66.5^\circ$ ) by measuring the angle ( $\alpha$ ) through which the plane of polarization is turned when a ray of polarized light is passed through a layer of the solution of known length.

It is readily hydrolysed by acids, and this process is commonly spoken of as the **inversion** of cane-sugar, and the product as **invert sugar**. These names are due to the fact that the hydrolysis is accompanied by a change in the optical activity of the solution. The solution of cane-sugar is dextro-rotatory, but after hydrolysis (or inversion) it becomes lævo-rotatory, as *d*-fructose is more strongly lævo- than *d*-glucose is dextro-rotatory.

Sucrose itself does not reduce *Fehling's* solution, but after inversion readily reduces. This would indicate that in the anhydride formation the aldehydic group of *d*-glucose and the ketonic group of *d*-fructose have been destroyed. The con-

stitutional formula suggested by *E. Fischer* (B., 1893, 2405), but since modified by *Haworth* (cf. Chap. LVI, B), is:

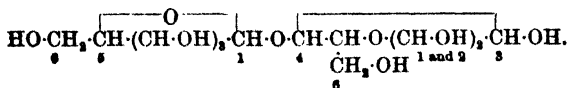


This formula readily accounts (a) for the formation of an octacetyl derivative (m.-pt. 67°) and an octamethyl ether; (b) for the absence of all reducing properties; (c) for the readiness with which it can be hydrolysed, since the two hexose molecules are united by means of an atom of oxygen; (d) for the non-formation of a hydrazone. For stereochemical configuration of this and other disaccharides cf. Chap. LVI, B.

**Milk-sugar** or **Lactose**, *Lactobiose*,  $\text{C}_{12}\text{H}_{22}\text{O}_{11} + \text{H}_2\text{O}$ , occurs in milk of most animals, and only occasionally in the vegetable kingdom. Cow's milk contains about 4 and human milk 6-8 per cent. It is obtained by evaporating the whey formed in cheese manufacture. It crystallizes in hard rhombic prisms, and is much less sweet than cane-sugar, and also much less soluble in water. It is converted into "lacto-caramel" at 180°. It shows muta-rotation (p. 350), reduces *Fehling's* solution, yields an osazone and gives an acid containing the same number of carbon atoms, and hence contains the CHO group. The anhydrous sugar occurs in  $\alpha$  and  $\beta$  forms.

**Maltose** or **Malt-sugar**, *Maltobiose*,  $\text{C}_{12}\text{H}_{22}\text{O}_{11} + \text{H}_2\text{O}$ , is formed by the action of diastase upon starch during the germination of cereals (preparation of malt). It forms a hard white crystalline mass, very similar to grape-sugar, and strongly dextro-rotatory + 137°. It reduces *Fehling's* solution, but only to about two-thirds the extent to which *d*-glucose does.

Lactose and maltose resemble one another very closely, and are probably stereo-isomeric. Since they both possess reducing properties, yield hydrazones, cyanhydrins, and can be oxidized to monobasic acids containing the same number of carbon atoms, it is obvious that they must contain an aldehyde-group, and the following structural formula is assigned to both:



Lactose and maltose are not fermentable until after hydrolysis. Certain micro-organisms contain an enzyme **lactase** which hydrolyses the former, and it is then fermented by yeasts. After hydrolysis it can be converted into lactic acid by certain species of bacteria, and is fermented by a fungus (Kephir) to alcohol and carbon dioxide. Maltose is hydrolysed by the enzyme maltase.

In the formation of the lactose molecule it is the CHO or potential CHO group of the galactose which is utilized, as on oxidation **lactobionic acid**,  $C_{12}H_{22}O_{12}$ , is formed, and when hydrolysed this yields galactose and gluconic acid.

**Revertose** is the name given to the disaccharide obtained by *Croft-Hill* (J. C. S., 1903, 580) by the synthetic action of the enzyme maltase on *d*-glucose. It has  $[\alpha]_D = +91.5^\circ$ , and yields an osazone melting at  $173^\circ$  (corr.). It may be identical with *Fischer's* isomaltose (*E. F. Armstrong*, P. R. S., 1905, 76, B., 592).

**Cellobiose** or **Cellose** is a disaccharide,  $C_{12}H_{22}O_{11}$ , obtained by incomplete hydrolysis of cellulose (this Chap., C.) by means of acetic anhydride and sulphuric acid, in the form of its **octa-acetate**, m.-pt.  $228^\circ$ – $229^\circ$ . Yield 50 per cent. The sugar itself obtained by hydrolysing the acetate with alcoholic potash forms a colourless crystalline powder practically insoluble in alcohol or ether. It reduces *Fehling's* solution, exhibits mutarotation, has  $[\alpha]_D = +34.6^\circ$ , is not fermented by yeast, and on hydrolysis with acids yields *d*-glucose. It is hydrolysed by maltase, and by an enzyme contained in apricot kernels and termed **cellase**. Its **osazone** melts at  $208^\circ$ – $210^\circ$ , and bromine water oxidizes the sugar to **cellobionic acid**.

**Gentiobiose** is a reducing disaccharide obtained by incomplete hydrolysis of the tri-saccharide, gentianose, with 0.2 per cent sulphuric acid or invertase. It melts at  $190^\circ$ – $195^\circ$ , has a bitter taste, and shows mutarotation; the final value is  $[\alpha] + 9.8^\circ$ . It is not fermented by yeast.

**Trehalose**,  $C_{12}H_{22}O_{11}$ ,  $2H_2O$ , is a non-reducing sugar found in fresh moulds and in manna. It is non-reducing, and has  $[\alpha]_D = +197^\circ$ , and on hydrolysis it yields *d*-glucose.

**Isomaltose** was obtained synthetically by *E. Fischer* (B., 1895, 3025) by the condensing action of hydrochloric acid on glucose. It is non-fermentable and yields an **osazone** with m.-pt.  $150^\circ$ .

**Melibiose**,  $C_{12}H_{22}O_{11}$ ,  $2H_2O$ , one of the hydrolytic products

of raffinose when dilute acids or top yeasts are used, is a reducing sugar, is less sweet than cane-sugar, exhibits mutarotation,  $[\alpha]_D = +143^\circ$ , and on further hydrolysis yields *d*-glucose and *d*-galactose. Its osazone melts at  $178^\circ$ – $179^\circ$ .

Several disaccharides derived from *d*-glucose and *d*-galactose have been synthesized from *d*-aceto-chloro-glucose + *d*-galactose, and from *d*-aceto-chlor-galactose and *d*-glucose (B., 1902, 3145).

Others have been synthesized by enzymes (cf. Chap. LXIX, D3) *Bourquelot* has obtained gentiobiose, cellobioses and mannobiose and galactobiose.

Disaccharides derived from condensed hexose and pentose molecules are also known (B., 1898, 537; 1900, 2091; Bull. Soc., 1911, 9, 38, 84, 147).

**Raffinose** or *Melitriose*,  $C_{18}H_{32}O_{16} + 5H_2O$ , is found in the sugar-beet, and therefore in molasses, in the manna of the eucalyptus, and in cotton-seed cake, &c. It resembles cane-sugar but is tasteless, is strongly dextro-rotatory, and does not reduce *Fehling's* solution. When inverted, it yields in the first instance *d*-fructose and melibiose, the latter then breaking up into galactose and *d*-glucose.

**Gentianose**,  $C_{18}H_{32}O_{16}$ , is present together with cane-sugar in the fresh root of *Gentiana lutea*; it melts at  $207^\circ$ – $209^\circ$  (corr.), has  $[\alpha]_D + 31.5^\circ$ , it does not reduce *Fehling's* solution, and on hydrolysis yields gentiobiose and *d*-fructose, and finally fructose, glucose, and galactose.

**Stachyose**,  $C_{24}H_{42}O_{21} + 4\frac{1}{2}H_2O$ , which is found in the roots of *Stachys tuberosa* and of several *Labiatae*, and in Ash manna, is an example of a tetra-saccharide. Anhydrous, it melts at  $170^\circ$  and has  $[\alpha]_D = +149^\circ$ . Invertase, maltase, or acetic acid hydrolyse it, yielding *d*-fructose and **manninotriose**, and on further hydrolysis the latter yields *d*-galactose (2 mols.) and *d*-glucose (1 mol.).

### C. Polysaccharides

The empirical formula of the members of this series is  $C_6H_{10}O_5$ , but they all possess a much higher molecular weight, e.g.  $(C_6H_{10}O_5)_n$ . They are for the most part amorphous and tasteless, insoluble in alcohol and ether; a few are soluble in cold water, but the majority not; thus cellulose is insoluble

and also mucilage, the latter merely swelling up with water, while starch forms a jelly with hot water. When boiled with dilute acids or subjected to the action of enzymes, they are hydrolysed to mono- or disaccharides, generally to hexoses, e.g.  $C_6H_{10}O_5 + H_2O = C_6H_{12}O_6$ . The formation of pentoses is frequently to be noticed in this decomposition.

They must therefore be regarded as anhydrides of the monosaccharides. The hydrolysis proceeds in stages and intermediate products, such as cellulose in the case of cellulose and dextrines and maltose in the case of starch, have been isolated.

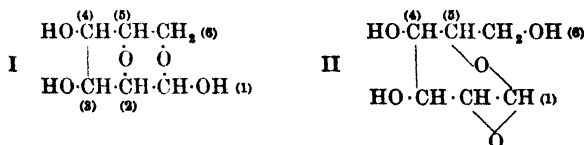
Although the polysaccharides are compounds of fundamental importance in the synthetic processes taking place in the living plant tissue, until recently very little was known about their constitution. The majority form colloidal solutions, and only very rough approximate molecular weights can be determined. They still contain free hydroxyl groups as they form esters with nitric and acetic acids, and ethers with methyl sulphate. The monosaccharide units which take part in the formation of these complex carbohydrates are: *d*-glucose, *d*-fructose, *d*-mannose, *d*-galactose, *l*-arabinose, *l*-xylose, and fucose. The investigations on the polysaccharoses have, to a large extent, been limited to studies of their hydrolysis, and, as they are so widely distributed in the vegetable kingdom, to the discovery of new commercial methods of utilizing them.

## Cellulose

This name has been given to a variety of different products from the vegetable kingdom. There are the celluloses proper, the compound celluloses, and the hemicelluloses.

The cellulose proper is met with in cotton-wool, linen, and Swedish filter-paper, and is best obtained by extracting filter-paper or cotton-wool successively with caustic potash, hydrochloric acid, water, alcohol, and ether. When air-dried it forms a white amorphous powder containing 6-8 per cent of moisture, which can be removed by gently warming under reduced pressure. At 150° cellulose begins to decompose, and when subjected to destructive distillation gives combustible gases, acetic acid, acetone, phenol, furfuraldehyde, and other products. When cellulose or starch is distilled under reduced

pressure at 200°–300°, appreciable amounts of  $\beta$ -glucosan, I (with m.-pt. 179° [ $\alpha$ ]<sub>D</sub> – 66.2°),



are formed; this can also be obtained from the glucosides of *Coniferae*, and cellulose is probably a condensation product derived from this (*Pictet and Saradin*, C. R., 1918, 166, 38). Isomeric with this  $\beta$ -compound is the  $\alpha$ -glucosan II (m.-pt. 108° and [ $\alpha$ ]<sub>D</sub> – 69.8 obtained by heating  $\alpha$ -glucose in a vacuum). They are both anhydrides of glucose and contain 2 oxide rings, the  $\alpha$ -compound in position 1 : 2 and 1 : 5 and the  $\beta$ -compound in 1 : 6 and 2 : 5.

Cellulose is insoluble in the ordinary reagents, but dissolves in an ammoniacal solution of cupric oxide (*Schweitzer's* Reagent), and is reprecipitated on the addition of acids, alkalis, or salts. (Cf. Artificial silk.) It also dissolves in a concentrated solution of zinc chloride. In the manufacture of Willesden goods the fabric is treated with zinc chloride solution so that only the surface fibres are attached and made waterproof. With iodine it gives a yellow or brown coloration, but in the presence of concentrated sulphuric acid a blue colour is developed. A simple glucose anhydride,  $\text{C}_6\text{H}_{10}\text{O}_5$ , **cellosan**, which is soluble in water is formed when cellulose triacetate is heated with naphthalene at 235° and acetyl groups subsequently removed. From lichnin acetate an isomeric **lichnosan** is formed.

Parchment-paper is unglazed paper which has been immersed for a very short time in concentrated sulphuric acid and then thoroughly washed; the acid transforms a superficial layer of the cellulose into **amyloid**. Hydrolysis with sulphuric acid gives first cellodextrins (cf. Starch dextrins), then a disaccharide cellobiose (p. 360), and finally *d*-glucose. Cellulose also gives a blue colour with a solution of iodine in zinc chloride and potassium iodide solution. It is usually estimated by *Cross and Bevan's* method, which consists in converting all other materials into soluble products by means of moist chlorine, then washing thoroughly and weighing the dried cellulose.

The following are the more important cellulose deriva-

tives, many of which are of considerable commercial value: **Cellulose hydrates**. These are products which closely resemble cellulose in composition, do not possess reducing properties, but are extremely hygroscopic. An important representative of this class is **mercerized cotton**, obtained by the action of cold, concentrated (15-25 per cent) sodium hydroxide on cotton. It is characterized by the readiness with which it can be dyed. **Hydrocelluloses**, obtained by the action of cold, concentrated acids, or by boiling with acetic acid containing 2 per cent of sulphuric acid, still retain their fibrous structure but are readily ground to a powder; they are less hygroscopic than cellulose and have pronounced reducing properties. **Oxycelluloses** are products formed by the action of oxidizing agents on cellulose. They dissolve in dilute sodium hydroxide solution, yielding golden-yellow solutions, have strong reducing properties, and appear to contain reactive carbonyl groups, and react with phenylhydrazine. They give a red coloration with aniline, and are less stable and more reactive than the celluloses proper. When boiled with hydrochloric acid they yield furfuraldehyde, which can be estimated by means of phloroglucinol. This reaction is used not merely for detecting but for estimating oxycelluloses. The oxycelluloses are widely distributed in nature, usually in the form of compound celluloses. Thus they are present in the celluloses from woods and lignified tissues generally, and are the chief constituents of the celluloses from cereal, straws, and esparto. According to *Henser* and *Hang* (*Z. Angew.*, 1918, **31**, 99, 103, 172), straw cellulose is a mixture of normal cellulose and pentosans, and is not a natural oxycellulose. It is highly probable that the substances termed cellulose hydrates, hydrocelluloses, and oxycelluloses are not chemical entities but mixtures of different products.

Cellulose gives rise to a **peroxide** when treated with bleaching powder, acidified ammonium persulphate, ozone, or other oxidizing agents. This is destroyed by treatment with sodium thiosulphate.

Cellulose is not normally digested in the human system but can undergo fermentation by means of certain species of bacteria. Certain species present in the intestines of *Herbivora* tend to form methane and fatty acids, and others hydrogen, but in both cases carbon dioxides and fatty acids (acetic and butyric) are also formed (*Langwill*, C. and I., 1932, 988).

## Industrial Applications of Cellulose and its Derivatives

Cellulose in the form of the cotton- and flax-fibre is the basis of the cotton and linen industries, and the paper industry is also based upon the use of cellulose: in the pure form as filter-paper and in the crude form as wood-pulp.

Large quantities of wood-pulp or sawdust are used for producing power alcohol (*Bergins*, C. and I., 1933, 1045) by first hydrolysing with 40 per cent HCl to glucose and then fermenting.

High-class rag paper is made by treating flax or cotton (rags, cotton waste, &c.) with dilute caustic soda, under pressure, and then bleaching, originally sun bleaching or, subsequently, bleaching with chlorine or bleaching powder. Such paper is very resistant, and when care is taken in using high-grade rags and careful washing to remove acid, can be preserved for centuries without deterioration, particularly in temperate climates. For printing purposes the moist paper is sized, e.g. with sodium resinate or alum, and is finally treated with gelatin to make the surface less porous.

The object of the treatment with alkali and also of the bleaching agent is to remove or bleach the non-cellulose constituents in the original fibre, as these are much more readily attacked than the cellulose proper.

With the increase in the demand for cheap paper other raw materials, e.g. esparto grass, straw, bamboo and wood-pulp have been introduced, and the result has been a considerable deterioration in the quality of paper and in its keeping properties. This is explicable when it is remembered that esparto cellulose is largely an oxycellulose which is far less resistant to chemical action than a true cellulose, and that mechanical wood-pulp contains all the lignin of the original wood.

Chemical wood-pulp is now usually made by digesting the disintegrated wood with calcium bisulphite under pressure. The bisulphite produces a disintegration of the lignin; after removal from the autoclaves the pulp is washed, bleached, and again washed, and is then ready for conversion into paper. High-grade paper is now usually made from a mixture of rags and chemical wood-pulp.



By-products are now obtained from the waste sulphite liquors. These can be evaporated and the residue subjected to destructive distillation for the production of acetone, methyl alcohol, &c., or they can be fermented by a special species of yeast and ethyl alcohol isolated (1 per cent of volume of liquor). (Cf. *Johnsen*, J. S. C. I., 1918, 129, T.)

Sodium sulphate mixed with sodium sulphide is also used for treating wood-pulp under pressure, and the product known as "sulphate pulp" is largely used in Scandinavia for manufacturing stout packing papers known as "Kraft paper".

**Cellulose Esters.**—As a polyhydroxy compound cellulose yields esters such as acetates, nitrates, &c.

The **acetylcelluloses**, or **cellulose acetates**, are of industrial value and are manufactured from mill waste or purified sawdust by treatment with acetyl chloride and zinc chloride or acetic anhydride and an acid. As esters they are readily hydrolysed to cellulose and acetic acid. They are used for photographic films, lacquers, plastics, collodion, and for artificial silk (rayon).

The **nitrates**, so-called **nitrocelluloses**, are made by the action of nitric and sulphuric acid on waste cellulose, and are not nitro-compounds but nitrates as they are hydrolysed to cellulose and nitric acid. Several products are known, differing in the amount of nitrogen present which varies with the concentration of the acids and the temperature used. In the manufacture it is necessary to remove all traces of acid by careful washing, otherwise the products decompose when kept. These esters form the basis of the collodion, celluloid, pyroxylin, gun-cotton, and artificial silk industries.

**Pyroxylin, Gun-cotton and Rayons.**—Pyroxylin is a nitro-cellulose containing 11.2–14.4 per cent of nitrogen and corresponding with 4 nitro-groups, and is the material utilized in making cellulose lacquers, paints and enamels, and is mixed with a plasticizer (e.g. tri-cresylphosphate) and a solvent such as butyl and amyl acetates, acetone, methyl ethyl ketone, butyl alcohol and often a gum or resin. **Collodion** with 10.8 per cent of nitrogen is used in medicine, &c., in the form of its solution in alcohol and ether (1:7). When mixed with camphor or certain phenolic ethers it forms ordinary **celluloid**, which is used for making toilet articles, accumulator cases, hand-rails, cutlery handles, &c. It is also the basis of nitro-cellulose films and rayons. For making artificial silk the solution is forced

from copper vessels through a fine orifice into water, when the fine threads are hardened, stretched, dried, wound, and then denitrated by treatment with ammonium sulphide or cuprous chloride and hydrochloric acid (*Chardonnel* process, 1883).

Other methods consist in (a) the use of cellulose acetates obtained by the action of acetic anhydride and a mineral acid on cellulose. The solution of the acetate in acetone is squirted into alcohol through small holes, 0.005 to 0.002 inch diameter (about 9 per cent of total rayon manufactured). (b) The use of a solution of cellulose in ammoniacal cupric oxide, and forcing the solution through small holes into dilute acid (*Pauly*, 1897). (c) Use of viscose. **Viscose** (*Cross and Bevan*, 1892) is the sodium salt of cellulose xanthate. High-grade sulphite wood-pulp or very short fibre cotton fibre is allowed to swell by treatment with sodium hydroxide solution, and is then shaken with carbon disulphide. Its solution in water forms a gelatinous mass which can be moulded. When exposed to the air it shrinks and hardens to a horn-like mass. It is used as a substitute for glue, celluloid, horn, ivory, &c. When used for the manufacture of artificial silk it is necessary to purify it; this is done by acidifying with a weak acid (acetic or lactic), precipitating with alcohol or brine, and washing. About 88 per cent of the world's rayon is made by this process. Attempts have been made to "animalize" viscose, i.e. to impart some of the properties of wool. One method consists in mordanting with quaternary ammonium compounds which are absorbed and then form lakes with the dye. Another is to incorporate casein (*Chap. LXVII*) with the fibre, and a third is to treat the fibre with a material which on heating forms a basic resin in or with the cellulose. Greater strength can be imparted to viscose fibre by stretching in the plastic condition (**Tenasco fibre**). **Viscoid** is a mixture of viscose with clay or zinc oxide, and sets to an extremely hard mass.

**Cellulose Ethers.\***—Two cellulose ethers used in industry are the **benzyl** and **ethyl** obtained respectively by the action of benzyl and ethyl chlorides on cellulose. They are not readily hydrolysed and are extremely water resistant. They are used in the lacquer, plastic and film industries.

\* *The Manufacture of Artificial Silk (Rayon)*, E. Wheeler, London, 1938. *Technology of Cellulose Ethers*, Warden, 3 vols., New York, 1933. *Plastics from Cellulose Materials*, C. and I., 1933, 341.

## Compound Celluloses

These comprise the natural products in which the cellulose molecules are united to those of a different type and include ligno-celluloses, pecto-celluloses, muco-celluloses, adipo-celluloses, and cuto-celluloses.

The **ligno-celluloses** are compounds of lignin or lignone,  $C_{19}H_{22}O_9$ , and cellulose, and are met with in jute and in most woods or lignified tissues of perennial stems. It is probable that the non-cellulose portion of the molecule consists of a cyclo-hexenedione.

In the pecto- and muco-celluloses the non-cellulose constituents are colloidal forms of carbohydrates or allied derivatives, hemi-celluloses, which are easily hydrolysed to pectin or pectic acids, and these readily gelatinize. The main flax fibre consists of pecto-celluloses, as does China grass or rhamie. In the adipo- and cuto-celluloses the cellulose is associated with fatty and waxy compounds of high molecular weight. The best-known representative is cork in which the cellulose is combined or mixed with cutin and suberin which appear to be glycerides of complex acids such as stearo-cutic. (For rafia see *Cross and Bevan*, J. S. Dyers, 1919, **35**, 70.)

The **hemi-celluloses** (C. and I., 1932, 968), or reserve celluloses are anhydrides of monosaccharides; they are not soluble in water but are readily hydrolysed by dilute mineral acids, to soluble monosaccharides, and in this respect differ from the celluloses proper. These products are usually mixtures containing *d*-mannose, *d*-galactose, *l*-arabinose, *l*-xylose, and occasionally *d*-fructose and *d*-glucose.

They are present in cell walls, and in seeds, especially in the husks of shells, e.g. peas, vetches, coffee beans, date stones.

Their main function is to serve as reserve cellulose, and during germination of the seed they are used up. Examples of hemi-celluloses are mannane, paramannane, galactane, &c.

## Starch or Amylum

This is present in the leaves of all assimilating plants, and is formed from carbon dioxide and water in sunlight under the influence of chlorophyll present in the chloroplasts of the cell.

It appears to be the final stage of synthesis, soluble sugars are first formed, most of these are transferred by the cell sap to the different parts of the plant for building up plant tissues and only the excess sugar is transformed into starch (*Brown and Morris*, J. C. S., 1893, 633), which is never present in large quantities in the leaves. In the absence of sunlight the starch in the leaves is hydrolysed to sugars (maltose) by the aid of the enzyme diastase, and passes into the sap, and is hence known as transitory starch. The great bulk of the starch is always found in the food reservoirs of the plant, e.g. rhizomes, tubers, and seeds; it is known as reserve starch, and it is from such sources that starch is always manufactured commercially. The starch in these reservoirs is built up from soluble sugars, probably sucrose (*Brown and Morris*), in the absence of carbon dioxide and sunlight by means of the leucoplasts of the cell, and numerous authorities have shown that some of the lower forms of plant life which are devoid of chlorophyll, e.g. *Spirogyra maxima*, *Bacillus coli*, can synthesize starch from such materials as sucrose, dextrose and glycerol, and in the absence of carbon dioxide certain forms of Algæ can make use of formaldehyde-bisulphite for synthesizing sugar. It is possible that there are slight differences between the starch of cereals and that of tubers; one of the differences being the mode of combination of the small amount of phosphorus present.

It forms a white, velvety hygroscopic powder, consisting of round or elongated granules built up of concentric layers around a nucleus or hilum, and the form and size of the granules vary considerably with starches from different sources. The granules of canna, potato, banana and sago starch are the largest, usually about  $60\mu$ , those from lentil, acorn, maize, and wheat are intermediate, and those from certain millets, oat and rice are the smallest (about  $15\mu$ ).<sup>\*</sup> In wheat starch the granules are nearly spherical and the hilum in the centre, those of the potato are egg or oyster shaped, with an eccentric hilum at the small end of the granule, and those from rice and maize are polygonal.

Potatoes contain 15-20 per cent of starch, wheat 60-65, maize 65, and rice 75-80. Arrowroot is obtained from the rhizomes of species of *Maranta* of the West Indies, and also from the root-stocks of *Curcuma angustifolia* in the East Indies.

<sup>\*</sup> For photo-micrographs see p. 92, Enyon and Lane's *Starch* (Heffer), 1928.

Sago is derived from the pith of the sago palm (*Sagus laevis*), and tapioca is prepared from the tubers of the cassava (*Manihot utilisima*) of the tropics.

Both the granules of starch and its jelly are coloured an intense blue by iodine and bright yellow by bromine. The colour of the iodide of starch vanishes on heating, but reappears on cooling. The coloration is used as a delicate test for traces of iodine or of starch. Ordinary air-dried starch contains some 10–20 per cent of water, some of which can be removed by heating to 105°.

Starch is insoluble in cold water, but when heated with water the granules swell and burst, forming a viscid opalescent liquid, **starch paste**, which sets to a stiff paste when cold. The temperature at which the change occurs is known as the temperature of gelatinization and varies from 55°–85°, and if the paste is allowed to stand for several days under aseptic conditions it gradually becomes more opaque and yields a deposit of amyloses. This is termed *reversion* and can be accelerated by acids or more particularly by the enzyme *amylcoagulase*.

Very little of a definite nature is known about the structure of starch although much work has been done on the subject. It is a carbohydrate complex and undergoes processes of hydrolysis when, (a) boiled with dilute sulphuric acid; (b) heated to a moderate temperature; (c) subjected to the action of a malted grain, e.g. barley, i.e. to the action of the enzyme diastase. *C. O'Sullivan* (J. C. S., 1872, 579; 1876, 125) showed that the products of diastatic fermentation are maltose and dextrin, and that the proportion of maltose in the product decreases as the temperature of conversion is raised above 63°. According to *Brown, Heron, and Morris* (1879, 596), malt extract at room-temperature converts starch paste into 80.9 parts of maltose and 19.1 parts of dextrin, and the same change occurs at all temperatures to 60°. The intermediate dextrins were investigated by *Brown and Morris* (1885, 527; 1889, 449, 462), and by *Brown and Millar* (1899, 286). Various views have been held as to the nature of the intermediate products and even of the final products. *Lintner* and *Düll's* view (B., 1893, 2533) that *Fischer's* iso-maltose (p. 360) is one of the final products is incorrect, the product being an impure maltose (*Ling, C. and I., 1937, 346*).

*Maquenne and Roux* (C. R., 1905, 140, 1303) claim that starch is a mixture of two substances *amylose* ( $\alpha$ -amylose) and

*amylopectin* ( $\beta$ -amylose), the former in the interior portion of the granule and the latter in the envelope. The amylose, obtained by reversion, or by heating starch with water under pressure and cooling, gives no coloration with iodine in the solid state, is not readily attacked by diastase, and is scarcely soluble in water at 120°; if, however, it is heated with water under pressure at 150° it dissolves fairly readily; the solution can be filtered, gives a blue coloration with iodine and is completely converted into maltose by malt extract at 56°. It is probable that the amylose and amylopectin are not homogeneous (1908, 146, 542). *Schryver* and *Thomas* (Bio. J., 1923, 17, 497) have found that certain starches contain small amounts of hemicelluloses, and according to *Ling* and *Nanji* (J. C. S., 1923, 2666), the ratio of amylose to amylopectin is constant and equal to 2:1, although their absolute percentages may vary according to the proportion of hemicellulose in the starch.

For the results of methylation of starch see *Irvine* and *Macdonald* (J. C. S., 1923, 898; 1924, 942; 1926, 1502). According to *Samec* and *Von Hoefft* (Koll., 1912, 132; 1913, 141; 1914, 23, 291), amylopectin owes its characteristics to the presence of a phosphoric acid complex. The amylopectin is a calcium salt and the first action of acid is to liberate the free complex acid which then undergoes hydrolysis, liberating phosphoric acid. The amount of phosphorus present is so small that if the phosphoric acid forms an integral part of the amylopectin molecule the latter must be at least 70,000.

**Uses of Starch.**—Starch is an important constituent of human food, and its hydrolysis to glucose and final oxidation to carbon dioxide and water supplies much of the heat required to maintain body temperature,



and to supply energy for muscular work. Wheat starch was used in the middle ages in the laundry and for stiffening fabrics, and in the eighteenth century for powdering the hair, and in this century potato-starch was introduced. In the nineteenth century the industry developed in an amazing manner, and both maize and rice were utilized as sources. Starch is used in the sizing of paper, as an adhesive in the manufacture of paste-boards, and in very large quantities in making sizes for treating cotton yarn before it is woven into

cloth, the objects being to bind loose threads, to strengthen the yarn, and to hold weighting materials such as china clay. The amount of size incorporated in the yarn varies enormously in different grades, and the starch mainly used is wheat and then potato. Starch, soluble starch and dextrin are also largely used for finishing the woven cotton fabric. Starch and dextrin are used as thickeners in colour printing on cotton as they serve to increase the viscosity of the dye solution. Very large quantities are used for dressing and finishing fabrics after laundering. It is also used as a constituent in custard powders, ice-cream powders and toilet powders, and is the source from which large amounts of glucose and dextrin are manufactured (for manufacture of starch and starch products, soluble starch, dextrins and glucose cf. *Eynon and Lane*, Chap. VI-XI).

Soluble starch is formed (a) by leaving starch in contact with cold mineral acids, (b) by heating starch with glycerol, (c) by boiling starch with water containing a little sulphuric acid, (d) by the action of diastase on starch. Prolonged treatment with mineral acids converts starch into dextrins and maltose and finally into *d*-glucose (*Daish*, J. C. S., 1914, 2053, 2065; for detailed study of action of acids see *Nanji and Beazley*, J. S. C. I., 1926, 215, T.). Ordinary diastase or amylase, a  $\beta$ -diastase, converts starch finally into dextrins and maltose, whereas takadiastase, which contains the enzyme maltase in addition to an  $\alpha$ -diastase, yields *d*-glucose as final product. (*Davis and Daish*, Abs., 1914, ii, 588. Cf. *Baker and Hulton*, J. C. S., 1914, 1529; *W. A. Davis*, J. S. Dyers, 1914, 30, 249). Saliva and pancreatic juice also hydrolyse starch.

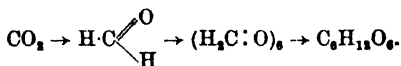
**Lichenin**, or *Moss starch*, present in many lichens, e.g. in Iceland moss (*Cetraria islandica*), is coloured a dirty blue by iodine; and **inulin**, present in the tubers of the dahlia and in the roots of chicory (*Inula Helenium*), is coloured yellow by iodine and converted into *d*-fructose when boiled with water.

**Glycogen**, or *Animal starch*, *Liver starch*, is present, e.g. in the livers of the mammalia, and is of great importance in animal metabolism; cf. Chap. LXIX, E. It is a colourless amorphous powder which is turned wine-red by iodine; after the death of the animal it rapidly changes into *d*-glucose, the same conversion being effected by boiling with dilute acids, while enzymes transform it into maltose. For preparation from yeast see *Harden and Young*, J. C. S., 1912, 1928.

**Dextrine**, or *Starch gum*, is a comprehensive name applied to

intermediate products obtained in the transformation of starch into maltose and *d*-glucose. It may be prepared (a) by heating starch either alone or with a little nitric acid, or, even better, in a vacuum at 120° over  $P_4O_{10}$ ; (b) together with *d*-glucose by boiling starch with dilute sulphuric acid; and (c) together with maltose by the action of diastase on starch. The dextrines are soluble in water, and are precipitated by alcohol. They are often named according to their reaction with iodine, e.g. **amylo-dextrine** blue, **erythro-dextrine** red, and **achroo-dextrine** no colour, and this order represents their relative complex structure, amylo-dextrin is nearest to starch and achroo-dextrin to maltose. They do not reduce *Fehling's* solution even when warmed, and are not directly fermentable by yeast but only after the prolonged action of diastase, glucose being formed as an intermediate product.

**Synthesis of Carbohydrates** (*Baly*, C. and I., 1932, 276; *Photo-synthesis*, E. C. C. Baly, London, 1940.—The sugars are extremely important from the point of view of plant physiology. The plant absorbs carbon dioxide and water, and with the aid of sunlight is capable, in the presence of chlorophyll, of transforming these into glucose and even more complex carbohydrates, such as starch, and oxygen, equal in volume to the carbon dioxide used, is evolved. Various speculations have been made with regard to the manner in which these complex compounds are formed. *Baeyer* has suggested that the carbon dioxide is first reduced to formaldehyde, and this then polymerizes as in *Loew's* experiments, yielding carbohydrates,



For many years the important link in this chain, viz. the reduction of carbon dioxide to formaldehyde, was missing; the reaction could not be accomplished in the laboratory. *Fenton* has shown (*J. C. S.*, 1907, 687) that when carbon dioxide is passed into water in which sticks of magnesium are immersed, a small amount of the gas is reduced to formaldehyde, especially in the presence of ammonia or phenylhydrazine. *Löb* has also found that moist carbon dioxide yields formaldehyde under the influence of the silent electric discharge (*Zeit. Elec.*, 1905, 745; 1906, 282).

More recently *Moore* and *Webster* (*P. R. S.*, 1914, B., 163,



556; 1918, B., 168) have proved that this reduction takes place in ultra-violet light (from quartz lamp) and *Baly, Heilbron and Barker*, who have made a more detailed study of this reaction (J. C. S., 1921, 1025) draw the following conclusions: (1) An aqueous solution of carbon dioxide gives formaldehyde when exposed to light of very short wave-length, and this aldehyde is polymerized to reducing sugars in light of slightly longer wave-length; (2) In the presence of sodium phenoxide or metallic salts such as ferric chloride or uranyl nitrate the aldehyde is formed but does not undergo polymerization; (3) The photosynthesis of formaldehyde can be photocatalysed by certain basic coloured substances, e.g. colloidal uranium and ferric hydroxides, malachite-green or methylorange, and the synthesis then takes place in visible light. The polymerization can be photocatalysed in a similar manner; (4) Carbohydrates, glycerol, acetone, &c., when exposed in aqueous solution to ultra-violet light yield formaldehyde and reducing sugar, and an equilibrium is established between sugar, formaldehyde and carbon dioxide. Chlorophyll appears to be an ideal photocatalyst for both stages of carbohydrate synthesis from carbon dioxide and water.

The synthesis of glucose from carbon dioxide and water is an endothermic reaction,



and the energy required is obtained by the absorption of light of suitable wave-length from sunlight.

*Grafe* (B., Bot. Ges., 1911, 29, 19) has shown that green seedlings can grow in an atmosphere containing 1.3 per cent of formaldehyde in the absence of carbon dioxide, and numerous authorities have proved the presence of small amounts of formaldehyde in assimilating leaves.

# CYCLIC COMPOUNDS

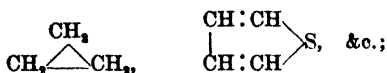
## XV. INTRODUCTION TO CYCLIC COMPOUNDS

The compounds which have been dealt with in Chapters I to XIV are derivable from the homologous hydrocarbons  $C_nH_{2n+2}$ ,  $C_nH_{2n}$ ,  $C_nH_{2n-2}$ , &c., by the exchange of hydrogen for halogen, hydroxyl or oxygen, amidogen, carboxyl, &c.; and may be described as **methane derivatives**.

As nearly all these compounds have open-chain formulæ, they are spoken of as **open-chain compounds**, **acyclic compounds** or **aliphatic compounds**.

In addition to this first class of organic compounds there is a second class, viz. the **closed-chain compounds**. The old classification was into aliphatic or methane derivatives and aromatic or benzene derivatives. The expression "aromatic" is historical, but no longer justified by facts, since compounds of agreeable as well as unpleasant odour are to be found in both classes. The members of this second class which are derivable from the hydrocarbon benzene,  $C_6H_6$  (and also from more complicated hydrocarbons such as anthracene, naphthalene, &c., which are themselves derivatives of benzene), just as the methane derivatives are from methane, are designated benzene derivatives.

Later investigations led to the discovery of numerous cyclic compounds which cannot be regarded as benzene derivatives, e.g.:



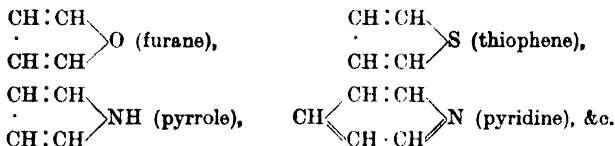
and hence the modern classification of the cyclic compounds is into:

**A. Carbocyclic, Alicyclic, or Isocyclic.**—In all these compounds the ring or closed chain is composed entirely of carbon

atoms. The carbocyclic compounds are usually divided into:

- (i) Polymethylene derivatives or naphthenes.
- (ii) Benzene derivatives or aromatic compounds, including the allied compounds naphthalene, anthracene, &c.

**B. Heterocyclic Compounds.**—In these compounds the closed ring is formed partly of carbon atoms and partly of atoms of other elements. Well-known examples are:

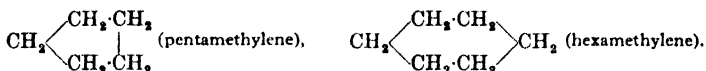
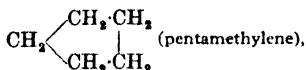
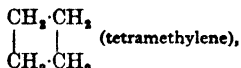
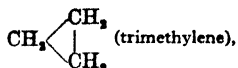


When a closed ring compound is formed from an aliphatic compound it usually contains 5 or 6 atoms forming the ring as there is, as a rule, less strain in such rings. This has already been illustrated in the formation of anhydrides from dibasic acids (Chap. X, A.), and in the formation of lactones from hydroxy acids (Chap. IX, A.) and of cyclic ethers (Chap. VIII, A.). Substituents in open-chain compounds often favour ring formation, thus methyl-succinic and -glutaric acids form anhydrides more readily than the parent acids. Similarly with the formation of lactones and cyclic ethers (cf. *Mills*, Thorpe's Dic., Supp. II, 452). The presence of end groups and their polarities often determine the formation of a closed ring, e.g. 1-chlor-6-aminohexane can give a 6-membered ring (6C + 1N). As a rule 5-membered rings are formed more readily than 6 in the case of anhydrides and lactones, but the opposite is true with the oxide form of the monosaccharides (cf. Chap. LVI, A.).

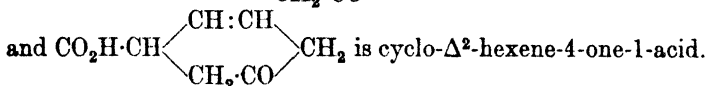
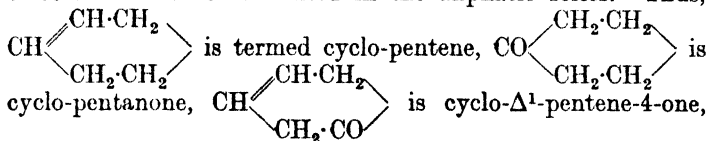
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## XVI. POLYMETHYLENE DERIVATIVES: CYCLOPARAFFINS

For summary of early work see *Perkin*, J. C. S., 1929, 1347. The hydrocarbons consist of three or more methylene groups united together to form closed rings. The specific names indicate the number of such groups, e.g.:



The systematic names for these compounds are **cyclo-propane**, **cyclo-butane**, &c., although the compounds are isomeric with the olefines, and have the same general formula,  $\text{C}_n\text{H}_{2n}$ . The above names indicate the fact that the compounds are in a sense saturated. The systematic nomenclature for derivatives is similar to that used in the aliphatic series. Thus,



**Relative Stability of Polymethylene Compounds.**—The simplest member is dimethylene (ethylene), which is the least stable of all the polymethylenes and forms additive compounds with great readiness. The majority of trimethylene derivatives are relatively unstable; to a certain extent they resemble ethylene oxide, and are capable of forming additive products by the rupture of the ring, e.g. bromine slowly transforms trimethylene under the influence of sunlight into trimethylene dibromide,  $\text{Br} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{Br}$ .

In certain reactions where only cyclo-propane derivatives might be expected, a mixture of both cyclo-propane and -butane compounds is formed (J. C. S., 1899, 48; 1901, 729, 1921, 1582; 1925, 387).

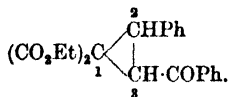
Tetramethylene derivatives are somewhat more stable, and penta- and hexa-methylene derivatives are quite stable and show little or no tendency towards the rupture of the molecule.

Reduction by *Sabatier* and *Senderens'* method (Chap. XLIX, A.), using hydrogen in presence of finely divided nickel, converts trimethylene into propane and tetramethylene into butane (*Willstätter* and *Bruce*, B., 1907, 3979, 4456). When, however, the 7 and 8 C-ring systems are reduced ring degradation occurs (Chap. XXXIV), thus cyclo-heptane yields a mixture of methyl-

cyclo-hexane and dimethyl-cyclo-pentane, and cyclo-octane yields dimethyl-cyclo-hexane (B., 1908, 1480). These facts are in harmony with *Baeyer's* tension theory. If the four valencies of the tetravalent carbon atom are assumed to be symmetrically distributed in space around the carbon atom, it is found that ring formation in the case of a cyclo-propane derivative can only take place by the exercise of a considerable strain in the molecule, viz. a deflection of  $+24^{\circ} 44'$ ; hence when the ring formation is completed there is considerable tendency for it to spring apart or rupture at some point. With penta- and hexa-methylene compounds, on the other hand, it can be seen by the aid of models that little strain is required to complete the ring formation, cyclo-pentane  $+0^{\circ} 44'$  and cyclo-hexane  $-5^{\circ} 16'$ , and thus the rings when once formed are relatively stable. For larger rings, e.g. Suberone with  $C_7$  and rings containing 20 or more C atoms, see Chap. XXXIII.

The number of carbon atoms constituting the ring is not the only factor which determines the ease of formation of a ring system or its relative stability when once formed. Rings containing a quaternary carbon atom are difficult to form, and when once formed are relatively unstable, a phenomenon well illustrated by a comparison of ethyl cyclo-propane-1 : 1-dicarboxylate and the isomeric 1 : 2-dicarboxylate (*Goldsworthy and Perkin*, J. C. S., 1914, 2665; *Kenner*, *ibid.* 2685).

A good illustration of the different ways in which a complex cyclo-propane derivative can undergo fission is met with in ethyl 2-phenyl-3-benzoyl-1 : 1-dicarboxylate:



Nascent hydrogen opens the ring between C atoms 1 and 3, yielding products of the type  $(\text{CO}_2\text{Et})_2\text{CH}\cdot\text{CHPh}\cdot\text{CH}_2\cdot\text{COPh}$ ; alkyl oxides, ammonia and amines produce a fission between atoms 1 and 2, so that compounds of the type  $(\text{CO}_2\text{Et})_2\text{CH}\cdot\text{C}(\text{COPh})\cdot\text{CHPh}$  are formed, and lastly, halogen hydrides dissolved in glacial acetic acid attack the union between atoms 2 and 3, and also that between 1 and 2, yielding respectively (a) and (b) (*Kohler*, J. A. C. S., 1917, 1404, 1699, 2405):

- (a)  $\text{CHPhBr}\cdot\text{C}(\text{CO}_2\text{H})_2\cdot\text{CH}_2\cdot\text{COPh}$  or  $\text{CHPhBr}\cdot\text{C}(\text{CO}_2\text{H})_2\cdot\text{CH}:\text{CPh}\cdot\text{OH}$ ,  
 (b)  $\text{CHPhBr}\cdot\text{CH}(\text{COPh})\cdot\text{CH}(\text{CO}_2\text{H})_2$ .

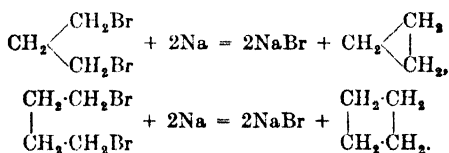
and these by the loss of  $\text{CO}_2$  and  $\text{HBr}$  yield respectively the

lactone,  $\text{CHPh}:\text{C} \begin{array}{l} \text{CH}:\text{CPh} \\ \text{CO}\cdot\text{O} \end{array}$ , and the unsaturated acid,  $\text{CHPh}:\text{C}(\text{COPh})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ .

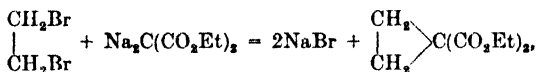
The cyclo-hexane compounds are the commonest as they are the hydrogenation products of benzene and its derivatives. The partially reduced benzene derivatives, e.g. tetrahydrophenol, dihydrobenzene, &c., are frequently referred to as hydroaromatic compounds and are discussed with the benzene compounds.

#### GENERAL METHODS OF FORMATION

1. By the action of sodium on dihalogen derivatives of the paraffins (*Freund*). The two halogen atoms must not be attached to the same or to adjacent carbon atoms.

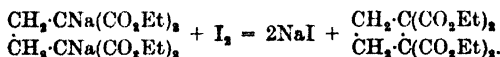


2. Acids and their esters can be obtained by the condensation of ethyl sodio-malonate with ethylene dibromide and other dihalogen derivatives (*W. H. Perkin, Jun.*):

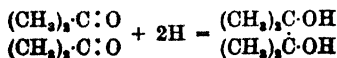


and the ester on hydrolysis yields trimethylene-dicarboxylic acid. Ethyl acetoacetate may be substituted for the malonate.

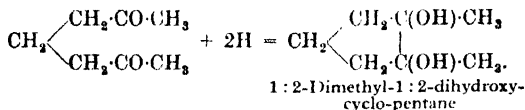
3. By the action of halogens (bromine, or preferably iodine) on the sodio-derivatives of certain esters, e.g. sodio-derivative of ethyl butane-tetracarboxylate (*W. H. Perkin, Jun.*):



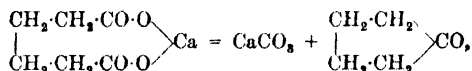
4. By intramolecular pinacone formation. Just as ketones on reduction yield pinacones:



(cf. p. 220), so certain diketones on reduction yield cyclic pinacones, i.e. dihydric alcohols derived from the polymethylene hydrocarbons:



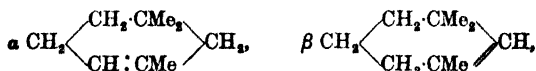
5. A number of ketones derived from the polymethylenes have been obtained by the dry distillation of the calcium salts of the higher dibasic acids of the oxalic series (*J. Wislicenus*), e.g. calcium adipate yields keto-pentamethylene:



and this can be reduced to pentamethylene. The constitution of the keto-derivative follows from the fact that on oxidation the ring is ruptured and glutaric acid is formed. Keto-hexamethylene and keto-heptamethylene, suberone, have been obtained by similar methods, but the yields are poor. Ketones containing 16 or even 30 carbon atoms in the ring are formed by using thorium salts of dibasic acids of high molecular weight (*Helv.*, 1926, 249, 499, cf. Chap. XXXIII).

6. Hexamethylene compounds are often obtained by the catalytic reduction of benzene derivatives with nickel as catalyst (cf. Chap. XLIX, A.). This is a method of commercial importance as the following products obtained by this method are commercial solvents; cyclohexanol (*sextol*) from phenol, methylcyclohexanol from cresol, and these on oxidation yield respectively cyclohexanone (*sextone*) and methylcyclohexanone (*sextone B*). *Sextate* is cyclohexanyl acetate.

7. Ring closure with formation of a 6-membered ring often occurs with certain dienes and olefinic alcohols. Examples are the conversion of geraniolene,  $\text{CMe}_2 \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHMe} \cdot \text{CH}_2$ , by means of sulphuric acid into  $\alpha$  and  $\beta$  cyclogeraniolenes,



and the conversion of linalool and geraniol into the terpene alcohol terpineol (Chap. LVII, A.). In the last case it is

essential that the olefine link and OH group shall be at opposite ends of the chain (*Hibbit and Linstead, J. C. S., 1936, 470*).

**General Properties.**—On the whole these compounds resemble the paraffins and not benzene as regards their chemical properties, hence the names cyclo-pentane for pentamethylene, cyclo-hexane, &c. Thus nitric and sulphuric acids tend to oxidize. Prolonged action of fuming sulphur acids tends to dehydrogenate and yield benzene derivatives (*A., 1923, 433, 350*).

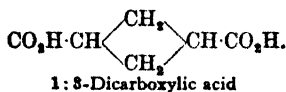
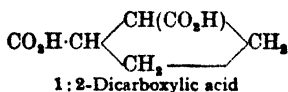
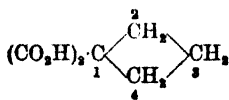
The trimethylene compounds, however, resemble the olefines, e.g. (a) they can combine with bromine to form additive compounds; (b) they are slowly oxidized by permanganate. In neither of these reactions do they take part so readily as the simpler olefines, and in all cases the products obtained are formed at the expense of the rupture of the ring.

The fact that the majority of the hydrocarbons of this series resemble paraffins indicates that the mere closing of the ring does not affect to any considerable extent the properties of a compound (cf. Benzene).

In their chemical properties the compounds closely resemble the corresponding derivatives of the paraffins, e.g. the acids resemble to a large extent the fatty acids, yielding salts, esters, acid chlorides, amides, &c.

The structure of a cyclo-hexane compound is often proved by an examination of the products formed on dehydrogenation (*Chap. XLIX, C.*), with Se or even with excess of bromine and  $\text{AlBr}_3$ . With Se an aromatic hydrocarbon is formed and with bromine a bromo-derivative of a benzene hydrocarbon. In these changes any alkyl substituents are unaffected.

**Isomerism.** (a) **Position Isomerism.**—No examples of isomerism have been met with in the case of mono-substituted derivatives, e.g. only one tetramethylenecarboxylic acid is known. Position isomerism can occur in the case of di- and poly-substituted derivatives, e.g. tetramethylene-1:1-dicarboxylic acid and isomeric 1:2 and 1:3 acids.

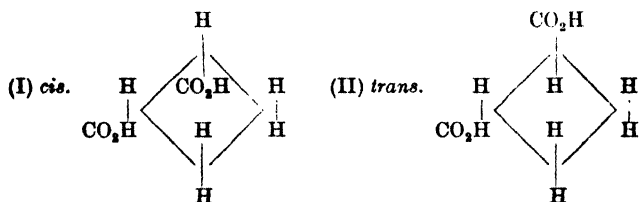




The number of isomerides possible in each case can be worked out by the student (cf. Benzene Derivatives).

(b) **Stereo-isomerism.**—In the tri-, tetra-, and penta-methylenes the C atoms lie on one plane and half the hydrogens in a plane parallel to this, and the other half in a third plane parallel to the other two. In cyclo-hexane it has been suggested that the ring is buckled so that all 6 C atoms are not in the same plane. But physical properties and examination of numbers of isomerides point to the planar configuration. Certain di-substituted derivatives have been found to exist in isomeric forms which are structurally identical. These must therefore be **stereo-isomeric**. Some of the simplest examples of this stereo-isomerism are met with in the dibasic acids. For example:

Tetramethylene-1:2-dicarboxylic acid exists in two isomeric forms. In both acids the  $2\text{CO}_2\text{H}$  groups are attached to the carbon atoms 1 and 2, and the only difference is in the relative spatial relationships of the groups. If the plane of the paper represents the plane in which the centres of gravity of the four carbon atoms of the ring lie, the possibilities are:



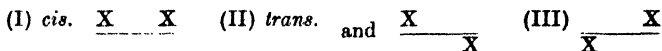
(I) That the two  $\text{CO}_2\text{H}$  groups lie in the same plane either above or below that of the paper (the *cis* acid); and (II) that the two  $\text{CO}_2\text{H}$  groups lie in different planes, one above and one below that of the paper (the *trans* acid). As a rule, the *cis* acids

yield inner anhydrides, e.g.  $\text{C}_4\text{H}_6$   $\text{O}$ , more readily than

the stereo-isomeric *trans* acids, and the *cis* acids are generally transformed into the corresponding *trans* acids when heated with hydrochloric acid at  $190^\circ$  (Perkin, J. C. S., 1894, 572).

A simple method of depicting these isomerides is due to Aschan (B., 1902, 3389). The plane of the carbon atoms of the ring is represented by a straight line. The unsubstituted hydrogen atoms are not denoted, only those which have been

replaced by substituents. It has been found that the symmetry of such projections corresponds with the symmetry of the molecules projected. For the *cis* dicarboxylic acids, for example, if  $\text{CO}_2\text{H} = \text{X}$ , we have:



The *cis* compound (I) has a plane of symmetry, whereas the *trans* compound (II) has not, only an axis of twofold symmetry so that corresponding with (II) is a third isomeride, which stands in the same relationship to (II) as an object to its mirror image, or as *d*- to *l*-lactic acids. Both should therefore be optically active (one *d* and the other *l* to the same extent), and should be capable of combining to yield a racemic compound. All the *trans* compounds prepared artificially are optically inactive, and are presumably therefore racemic compounds of (II) and (III), and a few, e.g. *trans* trimethylene-1 : 2-dicarboxylic acid and the tricarboxylic acid, have been resolved into optically active components by means of quinine (B., 1905, 3102).

Cyclo-pentane-1 : 2 : 3-tricarboxylic acid (Perkin and Robinson, J. C. S., 1921, 1392) exists in two *meso* forms, viz. *cis-trans-cis* and *cis-cis-cis* and a *racemic* form, *cis-trans-trans*, which can be resolved by brucine.

## XVII. BENZENE DERIVATIVES. INTRODUCTION

Benzene, which belongs to the group of hydrocarbon  $\text{C}_n\text{H}_{2n-6}$ , is much poorer in hydrogen than the paraffins, and the same holds good for its derivatives relatively, e.g. benzoic acid,  $\text{C}_7\text{H}_6\text{O}_2$ , with heptonic acid,  $\text{C}_7\text{H}_{14}\text{O}_2$ , and aniline,  $\text{C}_6\text{H}_7\text{N}$ , with ethylamine,  $\text{C}_2\text{H}_7\text{N}$ , &c.

The hydrogen atoms of benzene are, like those of methane, replaceable by numerous types of radicals. By the entrance of halogens, halide substitution products are formed, by the entrance of  $\text{NH}_2$ , aromatic bases, of OH, phenols, of  $\text{NO}_2$ , nitro-compounds, and of  $\text{CH}_3$ , &c., the homologues of benzene; there are, in addition to these, aromatic alcohols, aldehydes, acids, &c.

These benzene derivatives are in some respects analogous in their properties to the corresponding methane derivatives; they exhibit, however, characteristic properties of their own (see this Chap., A.). There exist mono- di-, tri-, &c., substituted benzene derivatives according as 1, 2, or more hydrogen atoms are replaced by the various radicals; thus, for instance, toluene,  $C_6H_5 \cdot CH_3$ , and chloro-benzene,  $C_6H_5 \cdot Cl$ , are mono-derivatives, dimethyl-benzene,  $C_6H_4(CH_3)_2$ , and dichloro-benzene,  $C_6H_4Cl_2$ , di-derivatives, and so on. It is not necessary that the substituents should be the same, so that innumerable compounds are known containing various substituents, e.g.  $OH \cdot C_6H_4 \cdot NO_2$ , nitro-phenol;  $C_6H_4Br \cdot SO_3H$ , bromobenzene - sulphonic acid;  $CH_3 \cdot C_6H_3(NO_2)_2$ , dinitro-toluene.

All the derivatives of benzene can be converted either into benzene itself or into very closely allied compounds by *relatively simple reactions*. Thus all the carboxylic acids of benzene (benzoic, phthalic, mellitic, &c.) yield benzene on distillation with lime, while other acids, such as salicylic, evolve  $CO_2$  and yield phenol; the last-named compound is converted into benzene when distilled with zinc dust. The homologues of benzene are converted by oxidation into benzene-carboxylic acids, which yield benzene when heated with lime.

*The relationship of a benzene derivative to its mother substance is therefore a very simple one.*

This circumstance is one particularly worthy of note, since the atomic group  $C_6H_6$  is comparatively complex and cannot readily be transformed into a simpler hydrocarbon containing 5, 4, or 3 carbon atoms; when oxidized, which is a matter of difficulty, it yields carbonic or similar simple organic acids.

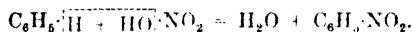
The relationships are such that it is comparatively easy to pass from one group of derivatives to another, e.g. the  $NO_2$  group is readily convertible into  $NH_2$ , and the latter is replaceable by halogen, hydrogen, and hydroxyl; the halogen is also replaceable by methyl, carboxyl, &c.

As a rule, the group of 6 carbons with the hydrogens is spoken of as the **benzene nucleus**, and all substituents are spoken of as **side chains**. Thus in  $C_6H_5 \cdot \underline{CHO}$ ,  $C_6H_4 \cdot \underline{(CH_3)_2}$ ,  $C_6H_5 \cdot \underline{NH_2}$  the radicals underlined are the **side chains**.

## A. Characteristic Properties of Benzene Derivatives

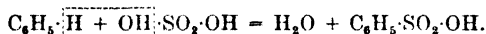
In many chemical properties benzene and its derivatives differ markedly from the paraffins or unsaturated open-chain hydrocarbons.

1. The aromatic hydrocarbons and their derivatives are readily attacked by concentrated nitric acid, yielding nitro-derivatives:



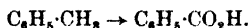
Certain of the higher paraffins also yield nitro-derivatives when heated with nitric acid (p. 105).

2. Sulphonic acids are readily formed by the action of concentrated or fuming sulphuric acid:



This type of reaction is never met with in the aliphatic series.

3. The homologues of benzene differ from the paraffins especially as regards oxidation; while the latter are only attacked with difficulty by oxidizing agents, the former are readily converted into benzene-carboxylic acids:



4. The halogens chlorine and bromine can react with benzene in two distinct ways: (a) yielding substituted derivatives, e.g.  $\text{C}_6\text{H}_6 + \text{Br}_2 = \text{C}_6\text{H}_5\text{Br} + \text{HBr}$ , or (b) yielding additive products, e.g.  $\text{C}_6\text{H}_6\text{Br}_6$ . Of these the process of substitution is the more important.

5. The halogen compounds  $\text{C}_6\text{H}_5\text{X}$  are chemically less active, and the hydroxyl compounds, e.g.  $\text{C}_6\text{H}_5(\text{OH})$ , are of a more acidic nature than the corresponding fatty bodies. The phenyl radical,  $\text{C}_6\text{H}_5$ , is therefore more acylous or "negative" in character than the ethyl,  $\text{C}_2\text{H}_5$ .

6. Diazo-compounds are far more common in the aromatic series than in the aliphatic.

## B. Isomeric Relations

1. Hexane can give several isomeric mono-substituted derivatives, e.g.  $\alpha$ ,  $\beta$ ,  $\gamma$ -chlorohexanes; benzene yields only one mono-derivative, e.g. only one chlorobenzene  $C_6H_5Cl$ . *The six hydrogen atoms of benzene thus possess an equal value, or are similarly situated within the molecule.* This is not merely an empirical law, but one which has been proved experimentally.

### PROOF OF THE EQUAL VALUE OF THE SIX HYDROGEN ATOMS

Let the 6 H atoms be designated as  $a$ ,  $b$ ,  $c$ ,  $d$ ,  $e$ , and  $f$  respectively.

(1) Phenol,  $C_6H_5(OH)$ , whose hydroxyl may have replaced the H atom  $a$ , can be converted into bromo-benzene,  $C_6H_5Br$ , and this latter into benzoic acid,  $C_6H_5(CO_2H)$ . The carboxyl in the latter has therefore also the position  $a$ , i.e. it has replaced the H atom  $a$ .

(2) Three hydroxy-benzoic acids,  $C_6H_4(OH)(CO_2H)$ , can either be prepared from benzoic acid or converted into it; their carboxyl therefore has the position  $a$ , and consequently their hydroxyl must replace some one of the other H atoms, be it  $b$ ,  $c$ , or  $d$ .

(3) Each hydroxy-benzoic acid can be decomposed, yielding carbon dioxide and ordinary phenol,  $C_6H_5OH$ :



And since the latter compound contains the hydroxyl in position  $a$ , according to (1), while the hydroxyl in the hydroxy-benzoic acids replaces the H atoms  $b$ ,  $c$ , and  $d$ , it follows that the hydrogen atoms  $a$ ,  $b$ ,  $c$ , and  $d$  are of equal value.

(4) For each H atom, i.e. each substituent X in a compound  $C_6H_5X$ , there are present two pairs of symmetrical hydrogen atoms, i.e. pairs of which either the one or the other atom may be replaced by any given radical without different substances resulting (p. 387). But the atoms of such a pair cannot both be present in the positions  $a$ ,  $b$ ,  $c$ , and  $d$ , as in this case three hydroxy-benzoic acids could not exist. It must therefore be the remaining H atoms  $e$  and  $f$  which are respectively in positions symmetrically situated to two of the former, and which are therefore of equal value with them, i.e.  $e = c$ ,

$f = b$ . Since, however,  $a = b = c = d$ , it follows that all the 6 hydrogen atoms are of equal value (*Ladenburg*, B., 1774, 1684).

2. With di-substituted derivatives of benzene it has been found that in each case three distinct isomeric forms exist. The two substituents may be alike, or they may be dissimilar, e.g. three dichloro-benzenes,  $C_6H_4Cl_2$ , three diamino-benzenes,  $C_6H_4(NH_2)_2$ , three dimethyl-benzenes,  $C_6H_4(CH_3)_2$ , three hydroxy-benzoic acids,  $C_6H_4(OH)(CO_2H)$ , are known. In no case have more than three such isomerides been found.

It can be shown that with respect to each H atom of benzene, e.g. for  $a$ , two pairs of other H atoms, e.g.  $b$  and  $f$ ,  $c$  and  $e$ , are symmetrically situated, so that it makes no difference whether, after  $a$  is replaced, the second substituent replaces the one or the other of the symmetrically placed hydrogen atoms, say  $b$  or  $f$ . According to the above notation, therefore,  $ab = af$ , and  $ac = ae$ . On the other hand, the combinations  $ab$  and  $ac$  are not equivalent, but represent isomers; the combination  $ad$ , the only remaining case, represents the third isomer.

#### PROOFS THAT FOR EVERY H ATOM ( $a$ ) TWO OTHER PAIRS OF SYMMETRICALLY LINKED H ATOMS EXIST

1. According to *Hübner* and *Petermann* (A., 149, 129; cf. also *Hübner*, A., 222, 67, 166), the (so-called meta-) bromobenzoic acid, which is obtained by brominating benzoic acid, and whose Br atom may be in position  $c$  and  $CO_2H$  in position  $a$ , yields with nitric acid two nitrobromo-benzoic acids,  $C_6H_3Br(NO_2)(CO_2H)$ , the  $NO_2$  being, say, in positions  $b$  and  $f$ . These are both reduced by nascent hydrogen to the same (so-called ortho-) amino-benzoic acid,  $C_6H_4(NH_2)(CO_2H)$ , the  $NO_2$  being here changed to  $NH_2$  and the Br replaced by H. Since the same amino-benzoic acid is formed in both cases, notwithstanding that the nitro-groups must be in the place of different H atoms, say  $b$  and  $f$ , from the fact of the two nitro-acids being dissimilar, it follows that  $b$  and  $f$  must be arranged symmetrically as regards the H atom  $a$ , i.e.  $ab = af$ .

2. In an analogous manner salicylic acid,  $C_6H_4(OH)(CO_2H)$ , which can be prepared from the above-mentioned amino-benzoic acid, yields two nitro-derivatives,  $C_6H_3(OH)(NO_2)(CO_2H)$ . If, however, the hydroxyl in these is replaced by hydrogen (a reaction which can be effected by indirect methods), the nitrobenzoic acids thus obtained,  $C_6H_4(NO_2)(CO_2H)$ , are identical,

and therefore the H atoms which have been replaced by  $\text{NO}_2$  are in positions symmetrical to  $a$ . When this nitrobenzoic acid is in its turn reduced to amino-benzoic acid,  $\text{C}_6\text{H}_4(\text{NH}_2)(\text{CO}_2\text{H})$ , it is not the above (ortho-) amino-acid (where  $ab = af$ ) which is obtained, but an isomer. The  $\text{NO}_2$  groups cannot therefore here be in the positions  $b$  and  $f$ , but must replace two other H atoms which are likewise symmetric towards  $a$ , say  $c$  and  $e$ , i.e.  $ac = ae$  (Hübner, A., 195, 4).

Thus two pairs of H atoms are symmetrically situated as regards the H atom  $a$ :  $ab = af$ ;  $ac = ae$ . The only other possible combination is  $ad$ , i.e. the sixth H atom has no other H atom corresponding with it relatively to  $a$ .

Nöelting (B., 1904, 1015) has shown that the 2-chloro-6-hydroxy-toluene and the 6-chloro-2-hydroxy-toluene obtained by the following reactions are identical:

1. 6-nitro-2-amino-toluene  $\rightarrow$  6-nitro-2-chloro-toluene  
 $\rightarrow$  6-amino-2-chloro-toluene  $\rightarrow$  6-hydroxy-2-chloro-toluene.
2. 6-nitro-2-amino-toluene  $\rightarrow$  6-nitro-2-hydroxy-toluene  
 $\rightarrow$  6-amino-2-hydroxy-toluene  $\rightarrow$  6-chloro-2-hydroxy-toluene.

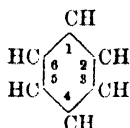
Cf. also Cohen, J. C. S., 1915, 847.

It has been assumed in the considerations just detailed that when one compound is converted into another by the exchange of atoms or radicals ( $\text{NH}_2$  for  $\text{NO}_2$ , H for OH), this exchange is effected without a so-called "molecular rearrangement" taking place at the same time (Chap. XXXVIII). Experience has proved that this may be taken for granted in a large number of reactions which proceed with relative smoothness and at comparatively low temperatures. Those instances in which a molecular rearrangement ensues are now well known; especially is this the case in the fusion of sulphonic acids with potash (exchange of  $\text{SO}_3\text{H}$  for OH), a reaction which takes place at relatively high temperatures only, and which frequently leads to isomers of the compounds expected. Other examples are: (a) potassium ortho-hydroxy-benzoate heated at  $200^\circ$  yields the potassium salt of the para-acid; (b) all three isomeric bromo-benzene-sulphonic acids,  $\text{C}_6\text{H}_4\text{Br}\cdot\text{SO}_3\text{H}$ , and the three bromo-phenols,  $\text{C}_6\text{H}_3\text{Br}\cdot\text{OH}$ , yield resorcinol or meta-dihydroxy-benzene,  $n\text{-C}_6\text{H}_4(\text{OH})_2$ , when fused with potash; (c) ortho-phenol-sulphonic acid when heated yields the isomeric para-acid,  $p\text{-OH}\cdot\text{C}_6\text{H}_4\cdot\text{SO}_3\text{H}$ . Reactions of this nature probably arise from the successive taking up and splitting off of atoms or atomic groups.

### C. Constitution of Benzene

The formula  $C_6H_6$  at once indicates that benzene cannot be a saturated open-chain compound. The possibility that it is an open-chain unsaturated compound containing several double or triple bonds has been shown to be untenable, e.g. dipropargyl (p. 58),  $CH:C\cdot CH_2\cdot CH_2\cdot C:CH$ , although resembling benzene in physical properties, is quite different as regards most of its chemical properties; it combines readily with bromine, yielding additive compounds with 2, 4, 6, or 8 atoms of bromine, and it is also oxidized with the greatest readiness. Benzene combines with bromine only slowly and under specific conditions, and then yields  $C_6H_5Br$ ; it is, further, extremely stable towards oxidizing agents. The equivalency of the 6 hydrogen atoms in the benzene molecule is a further strong argument against such open-chain formulæ. *Kekulé* was the first to suggest a closed-chain, cyclic, or ring formula for benzene.

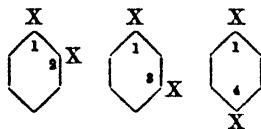
In order to account for the existence of only one mono-substituted derivative,  $C_6H_5X$ , but of three isomeric di-substituted derivatives,  $C_6H_4X_2$ , it is necessary to assume that a single hydrogen atom is attached to each carbon atom.



This formula is usually known as the benzene ring.

In the above formula the six hydrogen atoms are symmetrically placed with respect to one another, and thus in the formation of a mono-substituted derivative it is immaterial which one of the six hydrogens is replaced; only one compound,  $C_6H_5X$ , can be formed.

With di-substituted derivatives three isomerides are theoretically possible, viz.:



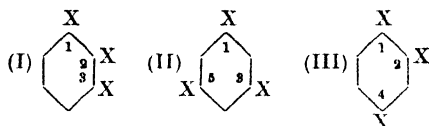
the 1 : 2 or ortho-compound, 1 : 3 or meta-compound, and the 1 : 4 or para-compound.



The compound 1 : 5 is identical with 1 : 3, and 1 : 6 is identical with 1 : 2. Cf. *Wohl*, B., 1910, 3474.

The hydrogen atoms in positions 2 : 6 form one pair of symmetrical hydrogen atoms mentioned on p. 387, and those in positions 3 : 5 form the second pair, whereas the hydrogen in position 4 has no other hydrogen atom corresponding with it.

Similarly, three tri-substituted derivatives,  $C_6H_3X_3$ , are known, and only three are possible with such a ring formula, viz.:

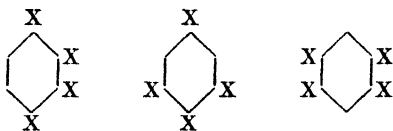


(I) 1 : 2 : 3 or adjacent tri-derivative. (II) 1 : 3 : 5 or sym. tri-derivative. (III) 1 : 2 : 4 or unsym. tri-derivative.

Any other combination is identical with one of these, 2 : 4 : 6 = 1 : 3 : 5 and 1 : 4 : 6 = 1 : 2 : 4.

The number of isomerides is considerably increased when the three substituents are not similar, e.g. in a compound,  $NH_2 \cdot C_6H_3Br \cdot CO_2H$ .

With a tetra-substituted derivative,  $C_6H_2X_4$ , where all four substituents are alike, only three isomerides are possible, namely, 1 : 2 : 3 : 4, 1 : 2 : 3 : 5, and 1 : 2 : 4 : 5.



And with a penta-substituted derivative,  $C_6HX_5$ , only one form is possible.

The number of isomerides actually found in each case is in perfect harmony with these theoretical deductions.

This ring formula represents each carbon atom as tervalent. Various ways of representing the atoms as quadrivalent have been suggested.

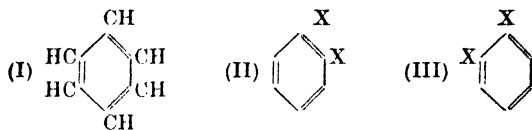
1. *Kekulé's* ring formula I with alternate single and double links.

This formula is in perfect harmony with the formation of benzene from acetylene, of *s*-trimethyl-benzene from acetone,

and of additive compounds by benzene and its derivatives, e.g. di-, tetra-, and hexa-hydro-derivatives,  $C_6H_8$ ,  $C_6H_{10}$ ,  $C_6H_{12}$  (p. 409); benzene hexachloride,  $C_6H_6Cl_6$  (p. 415); the triozone,  $C_6H_6O_3$  (Chap. XLVIII, G.), and an additive compound with ethyl diazoacetate.

Two arguments which have been brought forward against this formula are:

(a) Two ortho-disubstituted derivatives should be possible, namely, II and III:



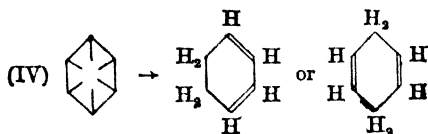
In (II) the 2 carbon atoms to which the substituents are attached are united by a double bond, and in (III) by a single bond. *Kekulé* has suggested that the single and double bonds may be continually changing, so that positions 2 and 6 are really symmetrical with respect to 1.

(b) The stability of benzene towards oxidizing agents. Di- and tetrahydrobenzenes—obtained by the reduction of benzene—which contain respectively two and one double bonds in their molecules, are readily oxidized, and also readily yield additive compounds with halogens. They also give quite different ultra-violet absorption spectra. Evidence based on other physical constants, such as molecular refraction, molecular volumes, molecular magnetic rotations, and heats of combustion, is inconclusive and conflicting. It has been suggested that the peculiar symmetrical structure of the benzene molecule may account for its stability, but the fact that cyclo-octatetrene,  $C_8H_8$  (Chap. XXXIII), which contains 8 CH groups united alternately with double and single linkings, has the properties of an aliphatic polyene and not of an aromatic compound, is a strong argument against the *Kekulé* formula (*Willstätter*, B., 1911, 3423; 1913, 517).

(II) A second method is represented by *Armstrong's* centric formula IV developed by *Baeyer*.

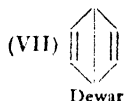
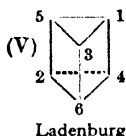
It represents the fourth valency of each carbon atom as directed towards the centre of the molecule, where the 6 are kept in equilibrium, a method of linking which is unknown in

the fatty series. When reduced to dihydro-benzene, four of the six centric bonds form two double bonds.



This readily accounts for the great difference between the chemical properties of benzene and of its reduction products.

Various other formulæ have been suggested for benzene, e.g. *Ladenburg's* prism formula, *Claus's* diagonal formula, and *Dewar's* formula.



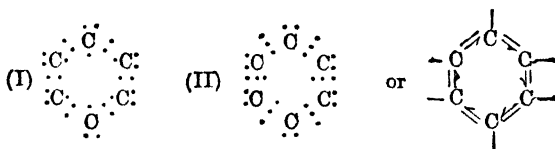
A strong objection to the prism formula and to any other three-dimension space formula is that the molecules of certain substituted derivatives would be dissymmetric, and should therefore exist in optically active modifications. No benzene derivative which occurs naturally is optically active, and attempts to resolve substituted benzene derivatives, e.g.  $C_6H(OH)(CO_2H)(CH_3)(C_2H_5)(NO_2)$ , nitrothymotic acid, have been unsuccessful.

Other objections to the prism formula are (a) the difficulty of accounting for the reduction products of benzene, and (b) the fact that when benzene is oxidized by various methods no compound is met with which contains a carbon atom attached to 3 other carbon atoms, as is the case in the prism formula.

The ring structure of the benzene molecule advocated by *Kekulé* in 1865 has been substantiated by all subsequent investigations, and the molecule must be represented by a symmetrical ring containing six CH groups in such a manner that the 6 hydrogens are equivalent. All the more recent work, particularly X-ray analyses of crystals, proves that substances like graphite, hexamethyl- and hexachloro-benzene have a planar structure and hence such formulæ as the prismatic, octahedral or *Sachs* are ruled out. The distance between two

adjacent carbon atoms has been shown to be 1.42 Å and the diameter of the ring to be 2.82 Å. The value 1.42 is less than that of the single link in the paraffin series, and only slightly more than that for the double carbon link. For a compound with the alternating single and double links the value should be the mean of the single or double. All positions and all valency bonds are equal to one another, and this high degree of symmetry may account for the great stability of the compound, a stability which is not quite so marked in heterocyclic and condensed ring compounds.

If the benzene molecule is not to be represented by the alternate single-double link formula of *Kekulé*, two possible methods of representing the structure on the electronic basis are: (1) The centric formula of *Armstrong* and *Baeyer*; (2) *Thomson*. In the former 6 electrons (1 from each carbon atom) are differentiated from the others and constitute a separate group. In the latter each carbon atom shares 3 electrons with its neighbour, or any two carbon atoms may be regarded as united by a covalent and a singlet link.



Such a formula is attractive from its simplicity, and is in harmony with most known facts, but is difficult to reconcile with modern views of wave mechanics of the covalent link (*Pauling*, J. A. C. S., 1931, 3228, also *Nature*, 1932, **129**, 973 and **130**, 273). In all probability benzene has a resonance structure between the two possible *Kekulé* formulæ (cf. Chap. LXXIII; also *Penny*, P., 1934, **146**, 233, *Ingold*, J. C. S., 1933, 1120). The centric formula presents difficulties when applied to condensed ring systems; but can be used in representing thiophene, pyridine, pyrrole, &c., and according to *Robinson* the characteristic of all benzenoid systems is the presence of 6 electrons forming a group which resents disruption (J. C. S., 1925, 1604).

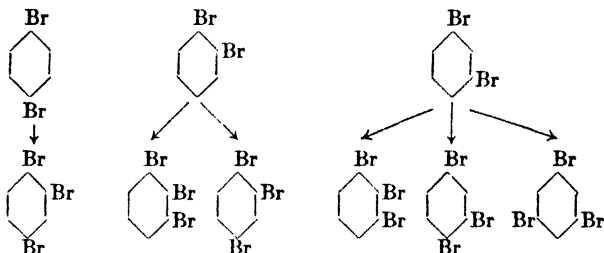
Certain reactions of benzene, e.g. formation of hydrides with 2H, 4H and 6H, formation of a triozone  $\text{C}_6\text{H}_6(\text{O}_3)_3$ , its oxidation to maleic anhydride and its combination with

ethyl diazoacetate, point to the presence of olefine or conjugate olefine links, and the tautomerism of compounds like *p*-nitrophenol with *p*-benzoquinone monoxine and of hydroxy azo-dyes with quinonephenylhydrazones are examples of anionotropic change characteristic of many unsaturated compounds (cf. Tautomerism, Chap. LIII).

It is possible that benzene in a static state has the centric structure, but in the presence of reagents of a polar type passes from the more symmetrical structure to the less symmetrical *Kekulé* structure.

#### D. Methods for determining which of three Isomeric Compounds is the Ortho, which Meta, and which Para

1. A method worked out by *Körner* (1875) for the three dibromobenzenes. One of these (*a*) is a solid melting at  $89^{\circ}$ ; a second (*b*) is a liquid which boils at  $224^{\circ}$ , and when solidified melts at  $-1^{\circ}$ ; and the third (*c*) is a liquid boiling at  $219^{\circ}$  and melting at  $+1^{\circ}$ . When further brominated, the compound *a* yields only *one* tribromobenzene; compound *b*, under similar conditions, yields a mixture of *two* isomeric tribromobenzenes; and compound *c* a mixture of *three*.



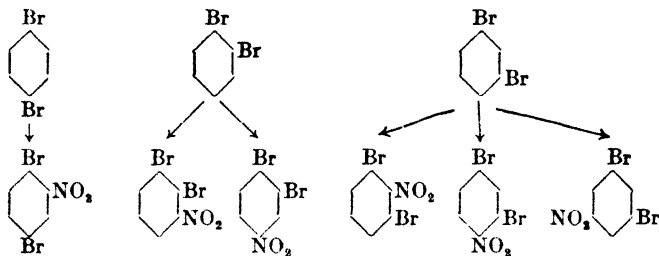
From a glance at the above formulæ, it is obvious (1) that the para- or 1 : 4-compound could give rise to only *one* tribromobenzene, (2) that the ortho- or 1 : 2-compound could give a mixture of *two* isomeric tribromobenzenes, and (3) that the meta- or 1 : 3-compound could give a mixture of *three* isomeric tribromobenzenes.

The compound melting at  $89^{\circ}$  is therefore *p*-dibromobenzene, the one boiling at  $224^{\circ}$  is the ortho-, and the one boiling at  $219^{\circ}$  and melting at  $+1^{\circ}$  is the meta-compound.

Incidentally, this gives a method for determining which of the three tribromobenzenes is the adj., which the sym., and which the unsym. A glance at the formulæ indicates that the sym.-tribromobenzene is the one which is formed from the *m*-dibromobenzene only. The adj. is the one formed from both ortho- and meta-, and the unsym. is the one which is formed from ortho-, meta-, and para-dibromobenzenes.

Similar results are obtained by examining the nitro-dibromobenzenes obtained by nitrating the dibromobenzenes.

The *p*-compound yields only one nitro-derivative; the *o*-compound yields two nitro-derivatives; the *m*-compound yields three nitro-derivatives:



but the nitro-dibromobenzenes thus formed are all different.

Similar methods may be adopted for determining the constitutions of the three diamino-benzenes,  $\text{C}_6\text{H}_4(\text{NH}_2)_2$ , by determining from how many of the six diamino-benzoic acids each of the three can be obtained by elimination of carbon dioxide.

The *m*-compound is the one which is formed from three distinct acids, the ortho- from two, and the para- from one only (*Griess*).

The relationships between the three xylenes,  $\text{C}_6\text{H}_4(\text{CH}_3)_2$ , and the six nitro-xylenes are exactly analogous to those between the three dibromobenzenes and their six nitro-derivatives.

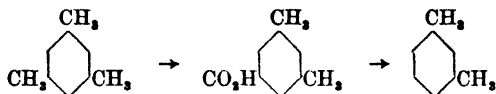
2. When the constitution of several groups of compounds, e.g. the dibromobenzenes, the xylenes, and the diamino-benzenes have been settled, then the constitutions of other compounds can be determined by conversion into one of the compounds of known constitution, e.g. the dinitro-benzene which yields *m*-diamino-benzene on reduction is the *m*-dinitro-

compound, or the acid obtained by the oxidation of *o*-xylene must be the *o*-dicarboxylic acid.

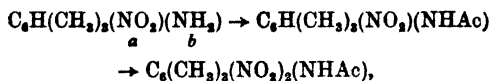


This constitution is confirmed by the fact that this acid is the only one of the three isomeric benzene-dicarboxylic acids which yields an inner anhydride, phthalic anhydride,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{O}$ , and hence the two  $\text{CO}_2\text{H}$  groups are probably attached to two adjacent carbon atoms.

3. The constitution of certain di-substituted derivatives is based on *Ladenburg's* proof (A., 179, 174) of the equivalence of the three unsubstituted hydrogen atoms in mesitylene,  $\text{C}_6\text{H}_3(\text{CH}_3)_3$ ; in other words, on the fact that mesitylene is sym.-trimethyl-benzene, e.g. the constitution of *m*-xylene is based on the following reactions:

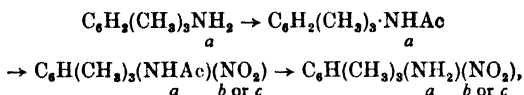


*Ladenburg's* proof is briefly as follows: Mesitylene yields a dinitro-derivative,  $\text{C}_6\text{H}(\text{CH}_3)_3(\text{NO}_2)_2$ , in which two of the three nucleus hydrogen atoms (*a* and *b*) are replaced by nitro-groups. From this is formed, by the three processes of reduction, acetylation, and nitration, a dinitro-acetamino-mesitylene:



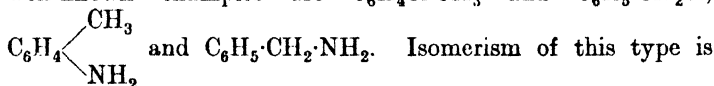
in which the third hydrogen (*c*) is replaced by  $\text{NO}_2$ ; on hydrolysis, this yields  $\text{C}_6(\text{CH}_3)_3(\text{NO}_2)_2(\text{NH}_2)$ , and on elimination of the amino-group,  $\text{C}_6\text{H}(\text{CH}_3)_3(\text{NO}_2)_2$ , a dinitro-mesitylene, which is identical with the original dinitro-compound started with. Hence two of the hydrogen atoms (say *b* and *c*) are similarly situated. The nitro-amino-mesitylene,  $\text{C}_6\text{H}(\text{CH}_3)_3(\text{NO}_2)(\text{NH}_2)$ , in which the nitro-group is in position *a* and the amino- in

position *b*, yields  $\text{C}_6\text{H}_2(\text{CH}_3)_3\text{NO}_2$ , and this, when reduced, acetylated, nitrated, and hydrolysed:



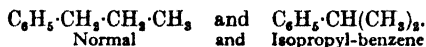
a nitro-amino-mesitylene which is identical with the original nitro-amino-mesitylene, and hence the position *a* is similarly situated to either *b* or *c*, but in the first part of the argument it was shown that  $b = c$ ,  $\therefore a = b = c$ .

**Other Types of Isomerism.**—1. In addition to the cases of isomerism dealt with in the preceding pages (isomerism due to the positions of the substituents in the nucleus), other types of isomerides are met with. A frequent example is the isomerism of a compound containing a substituent in the nucleus with a compound containing the same substituent in the side chain; well-known examples are  $\text{C}_6\text{H}_4\text{Cl}\cdot\text{CH}_3$  and  $\text{C}_6\text{H}_5\cdot\text{CH}_2\text{Cl}$ ,



usually accompanied by considerable difference in chemical properties.

2. "Side-chain isomerism" is the name given when the isomerism is confined to the side chain, e.g.:



**Stereo-isomerism.**—When the side chain contains an asymmetric carbon atom, e.g.  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})(\text{CO}_2\text{H})$ , mandelic acid, stereo-isomerism of the type of the active lactic acids is met with. Stereo-isomerism of the type of the crotonic acids is met with in unsaturated compounds like cinnamic acid,  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ , and stereo-isomerism analogous to that described in the case of polymethylene derivatives is met with among the reduced benzene derivatives, e.g. di-, tetra-, and hexahydrophthalic acid (Chap. XXVI, B.).

## E. Occurrence of the Benzene Derivatives

Many benzene derivatives occur in nature, e.g. oil of bitter almonds, benzoic acid, salicylic acid, and hippuric acid, while



others are obtained from the destructive distillation of organic substances, especially of coal.

The destructive distillation of coal yields (a) gases (illuminating gas); (b) an aqueous distillate containing ammonia and its salts, &c.; (c) coal-tar; and (d) coke.

**Coal-tar.**—Coal-tar is the chief source of benzene derivatives and is formed in the manufacture of coal-gas for illuminating purposes, and in “coke ovens” used for the production of high-grade coke for metallurgical purposes. In both cases coal is distilled from closed retorts at relatively high temperatures, about 1000° C., and the main difference between the two processes is the nature of the coal used. For gas-making a bituminous coal containing 32–40 per cent of volatile matter is used, and in order to obtain the maximum yield of hard coke bituminous coals containing from 18–32 per cent of volatile matter are employed.

The yields of products per ton of coal can be taken as:

	Gasworks		Coke Ovens
Gas .. .. .	10,000–12,000 cu. ft. =	17%	10·6%
Ammoniacal liquor ..	177 lb. =	7·9%	9·0%
Tar .. .. .	10 gall. =	5·0%	4·0%
Coke .. .. .	0·7 ton =	70·0%	71·5%

The tar from the two processes is much the same.

At the present time numerous low-grade coals, e.g. cannel coal, lignite or brown coal, and even bituminous shales, are distilled at comparatively low temperatures (500°–600° C.) in order to obtain oils, and, in the case of cannel coals, smokeless fuel for household purposes, **coalite**. The tar produced in all these cases is essentially different from the coal-tar obtained from gasworks and coke ovens. It consists largely of paraffin hydrocarbons, and is valueless for the manufacture of dye-stuffs, explosives, &c., but yields valuable illuminating and fuel oils and phenols (cf. C. and I., 1937, 895).

When coal-gas was first generally used for illuminating purposes (1813) the tar was regarded as a waste product, and could only be used as fuel, and its value as the source from which important synthetic dyes, perfumes, explosives, medicinal drugs and photographic developers could be manufactured was only gradually recognized. For many years after the introduction of coke ovens for the manufacture of metallurgical coke, the ammonia and tar formed at the same

time were not collected (so-called bee-hive ovens), but at the present time the great majority of the ovens are of the closed type, and are provided with by-product recovery plant. Still more recently, as the demand for benzene and toluene has increased, it has become customary to recover the benzene and toluene contained in the gas from the coke ovens, and even from the gas from gasworks, although this removal appreciably diminishes the illuminating power of the gas. The benzene hydrocarbons are usually removed by passing the gas through scrubbers containing creosote oil, which absorbs the hydrocarbons, and these can be afterwards isolated by heating the creosote oil or subjecting it to steam distillation. The amount of benzene and toluene in coal-gas is, roughly, about 15 times as much as that contained in the tar formed at the same time. In coke-oven gases the amount is only about half this. By this method of extracting benzene and toluene from the gases the amounts of these materials for the manufacture of explosives, &c., has been increased enormously.

Coal-tar contains as many as 200 different chemical substances; these are not present in the coal itself, but are formed during the distillation. During the past thirty years investigators have attempted to isolate compounds from coal itself by extraction with solvents, such as chloroform (*Keinsch*, 1910), pyridine (*Bedson*, 1908), benzene (*Pictet and Ram*, 1911), but so far few relationships have been established between the different materials present in coal and the chemical compounds present in tar (cf. *Tideswell and Wheeler*, J. C. S., 1919, 619). The chief components of coal are complex carbon compounds and not free carbon, and the first change during carbonization is to decompose the complex compound into simple, which may then react or polymerize, yielding the products found in the tar.

The most important compounds present in coal-tar are benzene, toluene, xylenes, phenol, cresols, naphthalene, and anthracene. Among the other compounds present are homologues of benzene, especially the methyl homologues; complex hydrocarbons, such as diphenyl, phenanthrene, fluorene, acenaphthene, chrysene and retene, indene and its homologues, and homologues of naphthalene; thiophene, benzonitrile, aniline, pyridine and its homologues; quinoline, isoquinoline, pyrrole, indole, carbazole, and acridine. Most of these are of little commercial importance, as the amounts present are small and their isolation from the tar is difficult.

Many of the hydrocarbons present in the tar are probably formed by the pyrogenic polymerization of acetylene, as this hydrocarbon when heated yields many of the products present in coal-tar (*R. Meyer and H. Fricke*, B., 1914, 2765).

The crude tar contains appreciable amounts of water, and has to be dehydrated before it can be distilled. Numerous methods are adopted, e.g. centrifuging the warm tar; heating the tar, allowing the water to rise to the surface, and removing it by a draw-off cock; or allowing the wet tar to come in contact with the hot vapour from another lot of boiling dehydrated tar.

The actual distillation is carried out in iron stills directly fire-heated. In many tar distilleries continuous stills are employed; in others intermittent distillation is used, the pitch being removed and a fresh charge of tar introduced from time to time.

The fractions collected vary in different distilleries, but, as a rule, in the first distillation the following are collected: (1) First runnings up to 105° or 110°; this contains water, ammonia, and some light oil. (2) Light oils up to 210°. (3) Middle oil or carbolic oil up to 240°. (4) Creosote oil up to 270°. (5) Anthracene oil above 270°. (6) Residue in the still = pitch.

The relative amounts of the different fractions vary considerably in different countries and different districts, but the following are fairly typical values for 1 ton of tar: Light oils, 12 gall.; carbolic oil, 20 gall.; creosote oil, 17 gall.; anthracene oil, 38 gall.; and pitch, 11 cwt. Calculated on 1 ton of tar, the yields of important products are: Benzene and toluene, 25 lb., or 1.1 per cent; phenol, 11 lb., or 0.5 per cent; cresols, 50 lb., or 2.2 per cent; naphthalene, 180 lb., or 8 per cent; creosote, 200 lb., or 8.8 per cent; and anthracene, 6 lb., or 0.27 per cent.

The light oils, including those from the first runnings, give rise to 60–65 per cent of benzene hydrocarbons, 12–15 per cent of naphthalene, 8–10 per cent of phenols, and 1–3 per cent of pyridine bases. The phenols are readily removed by treatment with caustic soda solution, and the pyridine bases by treatment with dilute mineral acids. The neutral substances, on further fractionation under varying conditions, yield 90 per cent benzol, 50 per cent benzol, 30 per cent benzol, and solvent naphtha. The numbers 90, 50, and 30 denote

the percentage of the oil which passes over below  $100^{\circ}\text{C.}$ , and not the actual benzene content of the oil. 90 per cent benzol contains 81 per cent of benzene, 15 per cent of toluene, 2 per cent of xylenes, and 2 per cent of impurities; and 30 per cent benzol contains respectively 13.5, 73.4, 11.7, and 11.7 per cent. From these crude benzols, by careful fractionation, pure benzene, toluene, and xylenes can be isolated.

In addition to the compounds, such as benzene, toluene, naphthalene, phenol, and anthracene, which are actually isolated and form important articles of commerce, a number of products consisting of complex mixtures are also manufactured. The most important of these are (1) benzol motor spirit, (2) solvent naphtha, which is used as a solvent for rubber in preparing waterproof fabrics and also for burning purposes, and (3) creosote oil, which is used in enormous quantities for pickling timber for use as railway sleepers, posts, and other purposes. Cf. Solvents from Coal-tars (C. and I., 1932, 28, 45).

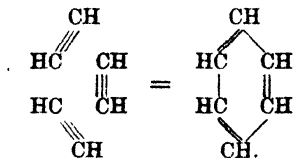
For hydrogenation of coal cf. *Bergius*, Chem. Age, 1927, 134, and for hydrogenation and cracking of coal-tar, C. and I., 1934, 816.

A large proportion of the tar is burnt as fuel, another large portion is used for the production of the above solvents and comparatively a small part refined to yield pure compounds used in chemical industry.

## F. Formation of Benzene Derivatives from Open-chain Compounds

The benzene derivatives can be produced from the fatty compounds by a relatively small number of reactions only.

1. Many methane derivatives, e.g. alcohol, yield a mixture containing a large number of the derivatives of benzene when their vapours are led through red-hot tubes. Acetylene,  $\text{C}_2\text{H}_2$ , polymerizes at a low red heat to benzene,  $\text{C}_6\text{H}_6$  (*Berthelot*):

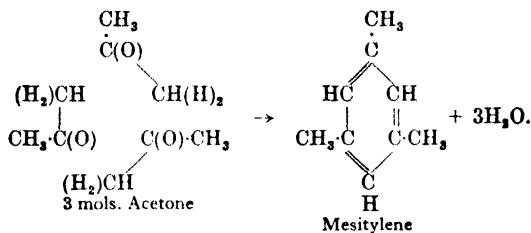


In an analogous manner allylene,  $\text{CH}_3\cdot\text{C}::\text{CH}$ , yields mesitylene or 1 : 3 : 5 trimethyl-benzene,  $\text{C}_6\text{H}_3(\text{CH}_3)_3$ , when distilled

with dilute sulphuric acid, while crotonylene,  $\text{CH}_3\cdot\text{C}::\text{C}\cdot\text{CH}_3$ , yields hexamethyl-benzene,  $\text{C}_6(\text{CH}_3)_6$ ; bromo-acetylene and iodo-acetylene polymerize to *s*-tribromo- and tri-iodo-benzene when exposed to light; propiolic acid,  $\text{CH}_3\text{C}\cdot\text{CO}_2\text{H}$ , polymerizes to trimesic acid,  $\text{C}_6\text{H}_3(\text{CO}_2\text{H})_3$ .

2. Natural gas, consisting largely of ethane and propane, when subjected to the process of "cracking" (p. 42), especially in the presence of metals, at various temperatures gives rise to aromatic hydrocarbons, and it has been suggested that these are the result of the following series of changes: ethane  $\rightarrow$  ethylene  $\rightarrow$  butadiene  $\rightarrow$  benzene (J. I. E. C., 1918, 901).

3. Ketones condense to benzene hydrocarbons when distilled with dilute sulphuric acid, e.g. acetone yields mesitylene (*Kane*, 1838) and methylethyl ketone, triethyl-benzene:



Hydroxy-methylene-acetone (p. 258) readily undergoes condensation, yielding triacetyl-benzene.

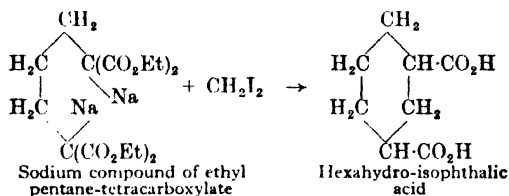
4. Certain 1 : 2-diketones, aldehyde acids, and keto-aldehydes are transformed in an analogous manner into benzene derivatives by suitable "condensing" agents; diacetyl,  $\text{CH}_3\cdot\text{CO}\cdot\text{CO}\cdot\text{CH}_3$ , is transformed by alkalis into xylo-quinone,  $\text{C}_6\text{H}_2\text{O}_2(\text{CH}_3)_2$  (B., 1888, 1411), and ethyl  $\beta$ -hydroxyacrylate into the ethyl ester of trimesic acid (B., 1887, 2930).

5. Certain 1 : 5 diketones react with hydrochloric acid, yielding reduced benzene derivatives, which can readily be transformed into benzene derivatives, e.g. ethylidene-diacetoacetic ester (from acetaldehyde and acetoacetic ester) yields dimethyl-

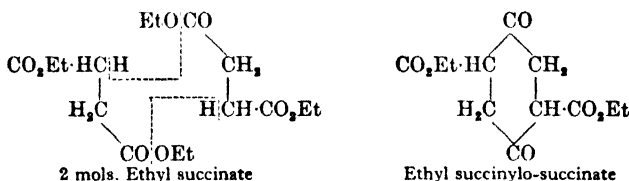
cyclo-hexenone,  $\text{CH} \begin{array}{c} \diagup \text{CO-CH}_2 \diagdown \\ \diagdown \text{CMe-CH}_2 \diagup \end{array} \text{CHMe}$ , the dibromide of which is converted into sym.-xylenol,  $\text{CH} \begin{array}{c} \diagup \text{C}(\text{OH})\text{:CH} \diagdown \\ \diagdown \text{CMe-CH} \diagup \end{array} \text{CMe}$  (*Knoevenagel*).

6. By the hydrolysis of the product from methylene iodide

and ethyl sodio-pentane tetracarboxylate, hexahydro-isophthalic acid is formed (*W. H. Perkin, J. C. S., 1891, 798*):



7. By the action of sodium upon ethyl succinate (*Herrmann*, or upon ethyl bromo-acetoacetate (*Duisberg*), ethyl **succinylo-succinate**, "ethyl cyclo-hexane-2:5-dione-1:4-diacid", is obtained, and is readily transformed into ethyl dihydroxy-terephthalate and then into quinol:



8. When ethyl sodio-malonate,  $\text{CHNa}(\text{CO}_2\text{Et})_2$ , is heated, ethyl phloroglucinol-dicarboxylate is formed, and this on hydrolysis yields phloroglucinol, which is also formed from malonyl chloride and acetone in the presence of calcium carbonate.

9. Hexyl iodide,  $\text{C}_6\text{H}_{13}\text{I}$ , is converted into hexachloro-benzene,  $\text{C}_6\text{Cl}_6$ , when heated with  $\text{ICl}_3$ , and into hexabromo-benzene,  $\text{C}_6\text{Br}_6$ , by bromine at  $260^\circ$ ; the latter compound can also be obtained by heating  $\text{CBr}_4$  to  $300^\circ$ .

10. Mellitic acid,  $\text{C}_6(\text{CO}_2\text{H})_6$ , is produced by the oxidation of graphite or lignite by means of  $\text{KMnO}_4$ .

11. Potassium carboxide, which is formed by the action of carbon monoxide upon potassium, is the potassium compound of hexahydroxy-benzene,  $\text{C}_6(\text{OH})_6$ .

12. For the conversion of hydroaromatic compounds into benzene derivatives see *Crossley* and others, *J. C. S.*, 1903, 110; 1904, 264; 1906, 875; 1914, 165.

THE CONVERSE TRANSFORMATION OF BENZENE  
DERIVATIVES INTO FATTY COMPOUNDS

1. When the vapour of benzene is passed through a red-hot tube it is partially decomposed into acetylene.

2. Benzene is oxidized by chloric acid to "**trichloro-phenomalic acid**", i.e.  $\beta$ -trichloroaceto-acrylic acid,  $\text{CCl}_3\cdot\text{CO}\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$  (*Kekulé and Strecker, A., 223, 170*).

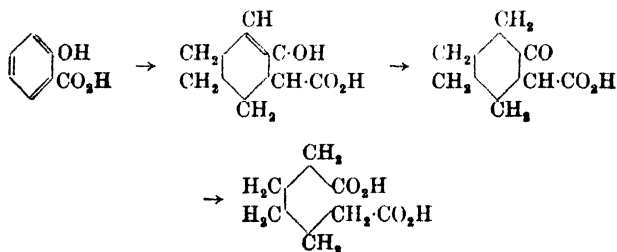
Chlorine and phenols react in the presence of alkali yielding chlorinated aliphatic acids, e.g. resorcinol (*m*-dihydroxybenzene) yields dichloro-maleic acid (B., 1894, 3364). Bromine, acting upon bromanilic acid, yields perbromo-acetone,  $\text{CBr}_3\cdot\text{CO}\cdot\text{CBr}_3$ .

3. Nitrous acid and catechol yield dihydroxy-tartaric acid (Chap. X, F.), and phenol and potassium permanganate yield tartaric and oxalic acids.

4. Benzene when oxidized with air in contact with vanadium pentoxide at  $250^\circ$ – $300^\circ$  yields much maleic acid with small amounts of benzoquinone which is probably an intermediate product.

5. The hexahydro-benzenes are transformed with difficulty into hydrocarbons of the methane series when heated with hydriodic acid at  $280^\circ$ .

6. When reduced with metallic sodium and amyl alcohol, *o*-hydroxy-benzoic acid is converted into pimelic acid:

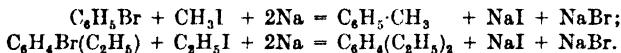


## XVIII. BENZENE HYDROCARBONS

A. Homologues of Benzene,  $C_nH_{2n-6}$ 

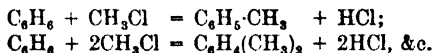
The benzene hydrocarbons are for the most part colourless liquids, insoluble in water, but readily soluble in alcohol and ether (durene and penta- and hexamethyl-benzenes are crystalline). They distil without decomposition, possess a peculiar and sometimes pleasant ethereal odour, and burn with a very smoky flame. Many, especially benzene and its methyl derivatives, occur in the lower fractions from coal-tar; others are prepared synthetically by *Fittig's*, *Friedel-Crafts'* or *Grignard's* method.

*Modes of Formation.* 1. *Fittig's Synthesis* (1864).—By the action of sodium on a mixture of an alkyl halide and an aryl bromide in dry ether:



*Jannasch* synthesized *p*-xylene, durene, and isodurene by this method, and the reaction is of value as establishing the constitution of the benzene homologues as the alkyl replaces the Br in the ring.

2. *Friedel and Crafts' Synthesis* (1877).—By the action of alkyl chlorides on aromatic hydrocarbons in the presence of anhydrous aluminium chloride:



This reaction is, like the preceding one, capable of very wide application; by means of it all the hydrogen atoms in benzene can be gradually replaced by methyl. The best yields are often obtained by the addition of carbon bisulphide, which serves as a diluent, and also prevents the temperature rising to any appreciable extent, and thus largely avoids the disintegrating action of the chloride on the homologues first formed. At higher temperatures, for example,  $C_6H_5\cdot CH_3$  is transformed to a large extent into  $C_6H_6$  and  $C_6H_4(CH_3)_2$  (B., 1894, 1606, 3235).



Formula	Name	Constitution Formula	Positions of Substituents	Melting-point	Boiling-point	Specific Gravity
$C_6H_6$	Benzene ..	$C_6H_6$	—	5.4°	80.4°	0.874
$C_7H_8$	Toluene ..	$C_6H_5 \cdot CH_3$	—	liquid	110	0.869
$C_8H_{10}$	<i>o</i> -Xylene ..	$C_6H_4(CH_3)_2$	1:2	-28	142	0.893
	<i>m</i> -Xylene ..	$C_6H_4(CH_3)_2$	1:3	-53	139	0.881
	<i>p</i> -Xylene ..	$C_6H_4(CH_3)_2$	1:4	+13	138	0.880
	Ethylbenzene ..	$C_6H_5 \cdot C_2H_5$	—	liquid	136	0.883
$C_9H_{12}$	Hemimellitene ..	$C_6H_3(CH_3)_3$	1:2:3	liquid	175	—
	Pseudo-cumene ..	$C_6H_3(CH_3)_3$	1:2:4	liquid	169.5	0.895
	Mesitylene ..	$C_6H_3(CH_3)_3$	1:3:5	liquid	163	0.865
	<i>o</i> -Methylethylbenzene ..	$C_6H_4(CH_3)(C_2H_5)$	1:2	liquid	159	—
	<i>m</i> -Methylethylbenzene ..	$C_6H_4(CH_3)(C_2H_5)$	1:3	liquid	159	—
	<i>p</i> -Methylethylbenzene ..	$C_6H_4(CH_3)(C_2H_5)$	1:4	liquid	162	—
	<i>n</i> -Propylbenzene ..	$C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_3$	—	liquid	158	0.867
$C_{10}H_{14}$	Cumene ..	$C_6H_5 \cdot CH(CH_3)_2$	—	liquid	153	0.866
	Durene ..	$C_6H_2(CH_3)_4$	1:2:4:5	80	193	—
	Isodurene ..	$C_6H_2(CH_3)_4$	1:2:3:5	—	196	—
	Metacymene ..	$CH_3 \cdot C_6H_4 \cdot CH(CH_3)_2$	1:3	—	175	0.862
	Cymene ..	$CH_3 \cdot C_6H_4 \cdot CH(CH_3)_2$	1:4	—	175	0.856

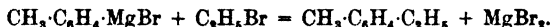
Zinc, antimony, and ferric chlorides (*Nencki*, B., 1899, 2414; *Menschutkin*, Abs., 1904, i, 188, 673) act in the same way as chloride of aluminium, while ethyl chloride and other halide compounds, such as chloroform and acid chlorides, may replace methyl chloride. Good yields of mono-alkyl derivatives are usually obtained when an excess of hydrocarbon is used; with excess of alkyl chloride 2 or 3 alkyl groups may be introduced. During the reaction molecular rearrangement can occur, thus benzene and *n*-propyl chloride yield isopropylbenzene unless low temperatures are used. With a compound like  $C_6H_5 \cdot CH_2(CH_2)_2 \cdot CH_2Cl$  the  $AlCl_3$  will induce internal condensation yielding the compound  $C_6H_4$   $\begin{array}{c} \diagup CH \cdot CH_2 \\ | \\ \diagdown CH \cdot CH_2 \end{array}$  tetrahydronaphthalene.

For further discussion see Chap. XLIX, G.

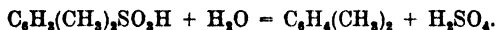
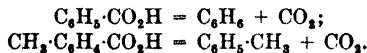
Alcohols also, like the alkyl halides, can react in an analogous manner in presence of  $ZnCl_2$ :



3. Another synthetical method is by the action of an alkyl iodide (bromide or sulphate) upon the *Grignard* compound derived from an aryl bromide in toluene solution (*Houben*, B., 1903, 3083; 1904, 488; *Werner*, *ibid.* 2116, 3618):



4. The benzene hydrocarbons are formed when their carboxylic acids are distilled with soda-lime:



5. The  $SO_3H$  group of a sulphonic acid (Chap. XXIII) can be eliminated by dry distillation, by heating with concentrated hydrochloric acid to  $180^\circ$ , by distillation of the ammonium salt (*Caro*), or by treatment with superheated steam, e.g. in presence of concentrated sulphuric acid (*Armstrong*, *W. Kelbe*); also by heating with concentrated phosphoric acid.

6. From the amino-compounds by transforming these into

diazonium-compounds (Chap. XXII, A.), and boiling the latter with absolute alcohol or with an alkali stannite solution.

7. By distillation of the phenols (or ketones) with zinc dust.

*Isomers and Constitution.*—The table given on p. 406 shows that the benzene hydrocarbons, from  $C_8H_{10}$  on, exist in many isomeric modifications; thus, isomeric with the three xylenes we have ethyl-benzene, with the three trimethyl-benzenes, the three methylethyl-benzenes and the two propyl-benzenes.

The constitution of these hydrocarbons follows very simply from their modes of formation. A hydrocarbon  $C_{10}H_{14}$ , for instance, which is obtained from benzene and methyl chloride by the *Friedel-Crafts* reaction, can only be a tetramethyl-benzene; another of the same molecular formula  $C_{10}H_{14}$ , which has been prepared from bromo-benzene, butyl bromide and sodium, must be a butyl-benzene; while a third, from *p*-bromo-toluene, normal propyl iodide and sodium, must be a *p*-propyl-toluene (*p*-methyl-*n*-propyl-benzene), &c. The synthesis therefore determines the constitution.

The groups  $CH_3$ ,  $C_2H_5$ , &c., which replace hydrogen in benzene, are termed "**side chains**".

When oxidized, the hydrocarbons yield a benzene-mono-, di-, or tri-, &c., carboxylic acid, e.g. benzoic acid,  $C_6H_5\cdot CO_2H$ , *o*-, *m*-, *p*-phthalic acid,  $C_6H_4(CO_2H)_2$ , according to the number of side chains present in the hydrocarbon; and a further proof of the constitution of the compound is thus afforded.

If, for example, a hydrocarbon  $C_9H_{12}$  yields a benzene-tricarboxylic acid,  $C_6H_3(CO_2H)_3$ , upon oxidation, it must contain three side chains, i.e. must be a trimethyl-benzene; should a phthalic acid, on the other hand, result, then it can only be an ethyl-toluene. Since cymene yields *p*- (or tere-) phthalic acid,  $C_6H_4(CO_2H)_2$ , on oxidation, its two side chains must be in *p*-positions to one another.

The respective isomers resemble each other closely in physical properties, their boiling-points, for example, lying very near together. The ortho-derivatives often boil at about  $5^\circ$ , and the meta- at about  $1^\circ$  higher than the para-compounds; the boiling-point rises with an increasing number of methyl groups (cf. B., 1886, 2513).

*Behaviour.*—1. The benzene hydrocarbons are, as a rule, readily nitrated and sulphonated, mono-, di-, and even tri-derivatives being all usually capable of preparation, according to the conditions. As a rule, it is only the hydrogen atoms

of the benzene nucleus which are replaced, the side chains reacting as paraffin residues. Hexamethyl-benzene can thus neither be nitrated nor sulphonated. Exceptions to this generalization are met with, e.g. mesitylene yields a nitro-derivative,  $C_6H_3(CH_3)_2 \cdot CH_2 \cdot NO_2$ ; cf. also Phenylnitro-methane, p. 424.

2. *Oxidation*.—Benzene itself is not readily oxidized; permanganate of potash converts it slowly into formic and oxalic acids, some benzoic acid and phthalic acid being produced at the same time. These doubtless result from some previously formed diphenyl.

The homologues of benzene, on the other hand, are readily oxidized to carboxylic acids, the benzene nucleus remaining unaltered, and each side chain—no matter how many carbon atoms it may contain—yielding, as a rule, a carboxyl group.

Nitric acid allows of a successive and often a partial oxidation of individual side chains, but varying amounts of nitro-compounds are also formed; chromic acid mixture ( $K_2Cr_2O_7 + H_2SO_4$ ) acts more energetically, converting all the side chains in the *p*- and *m*-compounds into carboxyl, and completely destroying the *o*-compounds. The latter may be oxidized to the corresponding carboxylic acids by alkaline  $KMnO_4$ . Chromyl chloride oxidizes to aldehydes (Chap. XLVIII, B.).

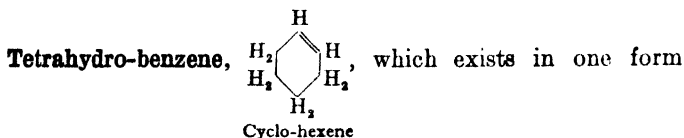
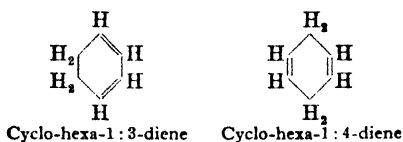
When a hydrocarbon is selectively oxidized, the longest side chain, as a rule, is most readily oxidized; thus  $C_3H_7 \cdot C_6H_4 \cdot CH_3$  yields first  $CO_2H \cdot C_6H_4 \cdot CH_3$ , and then  $C_6H_4(CO_2H)_2$ .

3. *Reduction*.—The benzene hydrocarbons and most of their derivatives are capable of taking up six atoms of hydrogen, and this is most readily effected by catalytic hydrogenation.

**Hexahydro-benzene (Cyclo-hexane)** and its homologues,  $C_nH_{2n}$ , are colourless liquids insoluble in water, and of somewhat lower boiling-point than the corresponding benzene hydrocarbons. They resemble paraffin hydrocarbons in properties and can be dehydrogenated to aromatic hydrocarbons by sulphur. With fuming nitric acid they yield nitro-derivatives of benzene. They are found in petroleum, especially in that from the Caucasus (*Beilstein, Kurbatow*).

The partially reduced benzene derivatives behave more like olefines. The **dihydro-benzenes**,  $C_6H_8$ , readily combine with two or four atoms of bromine, and are readily oxidized by alkaline permanganate, as might be inferred from the

presence of double bonds in the molecule. Two isomeric dihydro-benzenes are known, viz.:



only, is readily oxidized, combines with two atoms of chlorine and bromine or with a molecule of hypochlorous acid. All are colourless, volatile liquids.

4. *Behaviour with Halogens*.—Chlorine and bromine react differently, according to the conditions. In direct sunlight they yield with benzene the additive products  $C_6H_6Cl_6$  and  $C_6H_6Br_6$ , while in diffused daylight, especially in presence of a little iodine,  $SbCl_3$  or  $MoCl_5$ , they give rise to the substitution products  $C_6H_5Cl$ ,  $C_6H_5Br$ , &c. (For further details, and for substitution by iodine, see pp. 60 and 415.)

5. Chromium oxychloride,  $CrO_2Cl_2$ , converts the methylated benzene hydrocarbons into aromatic aldehydes (Chap. XXV, B., and XLVIII, B.; cf. B., 1890, 1070). (*Etard's reaction*.)

6. The numerous "condensations" which benzene, &c., can undergo with oxygenated compounds in presence of  $ZnCl_2$ ,  $P_4O_{10}$ , or  $H_2SO_4$ , and with chlorinated compounds in presence of  $AlCl_3$ , are of great interest; thus benzene yields diphenyl-ethane with aldehyde and sulphuric acid, and benzophenone with benzoic acid and phosphorus pentoxide.

7. In presence of aluminium chloride, oxygen can be introduced into benzene, yielding phenol; sulphur, yielding phenyl sulphide; ethylene, yielding ethyl-benzene; carbon dioxide, yielding benzoic acid.

**Benzene**,  $C_6H_6$ , was discovered by *Faraday* in 1825, and detected in coal-tar by *Hofmann* in 1845. It is obtained from the portion of coal-tar which boils at  $80^\circ$ – $85^\circ$  by fractionating or freezing. It may be prepared chemically pure by distilling a mixture of benzoic acid and lime. The ordinary benzene of

commerce usually contains **thiophene**, and thus gives a characteristic deep-blue coloration when shaken with a solution of isatin in concentrated sulphuric acid; but it may be freed from the impurity by repeated shaking with small quantities of sulphuric acid, which converts the thiophene into a sulphonic acid. It burns with a luminous smoky flame, and is a good solvent for resins, fats, iodine, sulphur, phosphorus, &c. When its vapour is led through a red-hot tube, diphenyl is obtained.

**C<sub>7</sub>H<sub>8</sub>.—Toluene, C<sub>6</sub>H<sub>5</sub>·CH<sub>3</sub>.** Discovered in 1837. *Formation*: by the dry distillation of balsam of Tolu and of many resins. *Synthesis* according to *Fittig* (see above). *Preparation*: from coal-tar, in which it is found accompanied by thio-toluene. Toluene is very similar to benzene. It boils at 110°, and is still liquid at -28°. CrO<sub>2</sub>Cl<sub>2</sub> converts it into benzaldehyde, and HNO<sub>3</sub> or CrO<sub>3</sub> into benzoic acid.

**C<sub>8</sub>H<sub>10</sub>.** (a) *o*-, *m*-, and *p*-**Dimethyl-benzenes** or **Xylenes**, C<sub>6</sub>H<sub>4</sub>(CH<sub>3</sub>)<sub>2</sub>.—The xylene of coal-tar consists of a mixture of the three isomers, *m*-xylene being present to the extent of 70 to 85 per cent. They cannot be separated from one another by fractional distillation. *m*-Xylene is more slowly oxidized by dilute nitric acid than its isomers, and can thus be obtained with relative ease. Benzene and toluene yield chiefly ortho-, together with a little para-xylene, when subjected to the *Friedel-Crafts* synthesis.

The pure xylenes can be obtained as follows: ortho from *o*-bromotoluene by *Fittig* reaction. Meta by oxidizing *s*-trimethylbenzene to mesitylenic acid, C<sub>6</sub>H<sub>3</sub>Me<sub>2</sub>·CO<sub>2</sub>H, and distillation with lime, the para compound from *p*-dibromobenzene by the *Fittig* reaction.

**Dihydro-*p*-xylene** can be prepared from ethyl succinylo-succinate. Liquid; b.-pt. 133°. It has an odour of turpentine, and is closely related to the terpenes (cf. *Baeyer*, B., 1892, 2122).

(b) **Ethyl-benzene**, C<sub>6</sub>H<sub>5</sub>·C<sub>2</sub>H<sub>5</sub>, is obtained from C<sub>6</sub>H<sub>5</sub>Br and C<sub>2</sub>H<sub>5</sub>Br by the *Fittig* reaction; from cinnamene, C<sub>6</sub>H<sub>5</sub>CH:CH<sub>2</sub>, on reduction with HI; and from C<sub>6</sub>H<sub>6</sub> and C<sub>2</sub>H<sub>5</sub>Cl by the *Friedel-Crafts* reaction. It is found in small quantity in the xylene from tar, and when oxidized yields benzoic acid.

**C<sub>9</sub>H<sub>12</sub>.** (a) **Trimethyl-benzenes**.—1. **Mesitylene**, 1:3:5-trimethyl-benzene, C<sub>6</sub>H<sub>3</sub>(CH<sub>3</sub>)<sub>3</sub>, is found in coal-tar along with the two other isomeric trimethyl-benzenes ("tarcumene"), and can be synthesized from acetone or allylene. It is a liquid of agreeable odour. Nitric acid oxidizes the side chains one

by one, while chromic acid mixture decomposes it completely. (For *constitution* see p. 396.)

2. **Pseudo-cumene**, 1 : 2 : 4-*trimethyl-benzene*, is separated from mesitylene, not by fractional distillation, but by taking advantage of the sparing solubility of pseudo-cumene-sulphonic acid. Its constitution follows from its formation from bromo-*p*-xylene [1 : 4 : 2], and also from bromo-*m*-xylene [1 : 3 : 4], by the *Fittig* reaction. Nitric acid oxidizes the side chains successively.

3. **Hemellithene**, 1 : 2 : 3-*trimethyl-benzene* (see B., 1882, 1853), is also present in coal-tar (B., 1887, 903).

(b) **Propyl-benzenes**. — 1. *n*-**Propyl-benzene**,  $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_3$ , is obtained from bromo-benzene and normal propyl iodide by the *Fittig* reaction, and also from benzyl chloride,  $C_6H_5 \cdot CH_2Cl$ , and zinc ethyl or  $Br \cdot Mg \cdot C_2H_5$ .

2. **Isopropyl-benzene** or **Cumene**,  $C_6H_5 \cdot CH(CH_3)_2$ , is produced by the distillation of cumic acid,  $C_6H_4(C_3H_7)(CO_2H)$ , with lime; from benzene and iso- or normal propyl iodide by means of  $AlCl_3$ , in the latter case with molecular rearrangement (p. 407); and from benzylidene chloride,  $C_6H_5 \cdot CHCl_2$ , and zinc methyl, this last method furnishing proof of its constitution. On oxidation, both compounds yield benzoic acid.

$C_{10}H_{14}$ . — (a) **Durene**, 1 : 2 : 4 : 5- or *s*-**tetramethyl-benzene**,  $C_6H_2(CH_3)_4$ , has been found in coal-tar, and can be prepared from toluene and methyl chloride by the *Friedel-Crafts* reaction, or from dibromo-*m*-xylene (from coal-tar xylene), methyl iodide, and sodium. It is a solid, and possesses a camphor-like odour. (For its *constitution* see B., 1878, 31.)

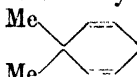
(b) **Methyl-propyl-benzenes**,  $C_6H_4(CH_3)C_3H_7$ . — The most important of these is **cymene** or **isopropyl-*p*-methyl-benzene**. It is found in Roman cummin oil (*Cuminum cyminum*), in eucalyptus oil, &c., and is formed when camphor is heated with  $P_2S_5$ , or better,  $P_4O_{10}$ , also when oil of turpentine is heated with iodine, &c. It has been synthetically prepared from *p*-bromo-isopropyl-benzene, methyl iodide, and sodium, and also from *p*-bromo-toluene, *n*-propyl iodide, and sodium, the *n*-propyl changing here into the isopropyl group. It is a liquid of agreeable odour.

Cymene was formerly regarded as *normal*-propyl-*p*-methyl-benzene, but its synthesis from *p*-brom-*iso*-propyl-benzene, methyl iodide, and sodium established its constitution as an isopropyl derivative (cf. *Widman*, B., 1891, 439). When oxi-

dized, it yields either *p*-toluic acid, terephthalic acid, cumic acid, or *p*-tolyl-methyl-ketone, according to the conditions.

$C_{12}H_{18}$ .—**Hexamethyl-benzene**, *Mellitene*, from methyl alcohol, acetone, and  $Al_2O_3$ , at  $400^\circ$ , crystallizes in prisms or plates which melt at  $164^\circ$ . It can neither be sulphonated nor nitrated.  $KMnO_4$  oxidizes it to mellitic acid,  $C_6(CO_2H)_6$ .

Compounds derived from the hydrocarbon,  $C_7H_8$ , isomeric with toluene but with a semi-cyclic olefine linking have been studied by *Auwers* (B., 1911, 1595; A., 1921, 425, 217), e.g.

 =  $CH_2$ . They are more volatile and have lower densities than the isomeric true benzenes, into which they readily pass in the presence of acids. They also readily polymerize and are termed **semi-benzene** derivatives.

## B. Unsaturated Benzene Hydrocarbons

The benzene hydrocarbons with an alkene group as a side chain may be regarded as aryl derivatives of olefines or even acetylenes, e.g.  $C_6H_5 \cdot CH:CH_2$ , styrene, or phenyl-ethylene;  $C_6H_5 \cdot C \equiv CH$ , phenyl-acetylene. They are formed by the elimination of  $CO_2$  from the corresponding acids, by the elimination of  $HBr$  from compounds of the type  $C_6H_5 \cdot CH_2 \cdot CH_2Br$ , and by the elimination of water from certain secondary and tertiary alcohols (C. R., 1901, 1182).

**Styrene** or **Cinnamene**,  $C_6H_5 \cdot CH:CH_2$ , occurs in storax (*Styrax officinalis*), in the juice of the bark of *Liquidambar orientale*, and in coal-tar. It is formed when cinnamic acid is slowly distilled or heated with water to  $200^\circ$ .

It is also obtained when benzene vapour and ethylene are passed through a red-hot tube, or when  $\alpha$ -chloro-ethyl-benzene,  $C_6H_5 \cdot CH_2 \cdot CH_2Cl$  (by action of chlorine on ethyl-benzene), is heated, or from coal-tar or synthetic ethylbenzene by a process of dehydrogenation (cracking). It is a liquid, has a characteristic odour, and boils at  $145^\circ$ , and is readily polymerized in sunlight or in presence of oxygen, but solutions in light petroleum can be kept for some time if a small amount of an antioxidant, e.g. quinol, is added. The polymerides of high molecular weight are of value in the Plastics industry (Chap. LX, Cl).



With HI it yields ethyl benzene, with HBr  $\omega$ -bromo-ethylbenzene  $C_6H_5 \cdot CH_2 \cdot CH_2Br$ , and with  $Br_2$  the dibromide, m.-pt.  $73^\circ$ .

**Phenyl-acetylene**,  $C_6H_5 \cdot C \equiv CH$ , from phenyl-propionic acid by the loss of  $CO_2$ , is a fragrant liquid, b.-pt.  $142^\circ$ , and yields white and pale-yellow explosive metallic compounds with solutions of silver and cuprous oxides. It combines with water to aceto-phenone,  $C_6H_5 \cdot CO \cdot CH_3$ , when it is dissolved in sulphuric acid, and the solution is diluted with water, or when heated with water to  $300^\circ$ . With *Grignard* compounds, it yields  $C_6H_5 \cdot C \equiv C \cdot MgBr$ , a reagent of use in synthesizing acetylenic alcohols.

Styrene derivatives are obtained by the action of *Grignard* reagents on aromatic ketones, e.g. aceto-phenone gives  $C_6H_5 \cdot CMe_2 \cdot OMgBr$  and then  $\alpha$ -methyl-styrene,  $C_6H_5CMe \cdot CH_2$ .

The aromatic hydrocarbons form definite compounds with picric acid (Chap. XXIV, A.), and these are frequently utilized for identifying particular hydrocarbons, and more particularly the more complex ones, diphenyl naphthalene, &c. The hydrocarbons also form similar additive compounds with *s*-trinitro-benzene.

## XIX. HALOGEN DERIVATIVES

		Cl		Br		I	
		M.-pt.	B.-pt.	M.-pt.	B.-pt.	M.-pt.	B.-pt.
$C_6H_5Cl$	.. ..	$-45^\circ$	$132^\circ$	$-31^\circ$	$156^\circ$	$-30^\circ$	$188^\circ$
$C_6H_4Cl_2$	<i>o</i> .. ..	liq.	179	-1	221	+27	286
	<i>m</i> .. ..	liq.	172	liq.	220	+40	285
	<i>p</i> .. ..	+56	173	+87	219	+129	285
$CH_2 \cdot C_6H_4Cl$	<i>o</i> .. ..	-34	159	-26	181	liq.	211
	<i>m</i> .. ..	-48	172	-40	184	liq.	204
	<i>p</i> .. ..	+7.4	173	28	185	+35	211.5
$C_6H_5 \cdot CH_2Cl$	.. ..	-48	179	—	199	+24	decomposes
$C_6Cl_6$	.. ..	229	326	—	—	—	—

Benzene and its homologues can give rise to (A) additive compounds with bromine or chlorine, or (B) substituted derivatives.

### A. Additive Compounds

These are of comparatively little importance; they are formed when the hydrocarbon is exposed for some time to chlorine or bromine vapour in bright sunlight, and are halogen derivatives of cyclo-hexane.

**Benzene hexachloride**,  $C_6H_6Cl_6$ , exists in two stereo-isomeric modifications; the one melts at  $157^\circ$ , and the other sublimes at  $310^\circ$ . When warmed with alkali, they yield trichloro-benzene and HCl. The **hexabromide** (*Matthews*, J. C. S., 1901, 43) melts at  $212^\circ$ .

### B. Substituted Derivatives

Numerous halide substitution compounds are known. They are either colourless mobile liquids or crystalline solids, insoluble in water but readily soluble in alcohol and ether, distil unchanged, and are distinguished by their peculiar odour and also, in part, by their irritant action upon the mucous membrane. They are heavier than water.

The halide compounds may be arranged in two distinct groups. In one the halogen is bound very firmly, far more so than in methyl chloride, ethyl iodide, &c.; it cannot be exchanged for OH (by means of AgOH), or for  $NH_2$  (by  $NH_3$ ), &c., but reacts with sodium (see the *Fittig* reaction, p. 405); A., 332, 38; and magnesium (see below). All the substituted derivatives of benzene and many common derivatives of its homologues belong to this class.

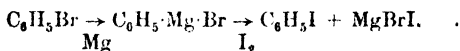
In the second group, of which benzyl chloride is a good type, the halogen atoms enter into reaction as readily as do those of the halide substitution products of the methane series.

When the members of the first group are subjected to oxidation, a process which converts side chains into carboxylic groups, chloro-derivatives of benzoic and other acids are obtained. The members of the second group, when subjected to similar treatment, yield aromatic acids which are free from halogen, e.g. benzoic acid,  $C_6H_5 \cdot CO_2H$ , phthalic acid,  $C_6H_4(CO_2H)_2$ . From this it follows that the halogen is present in the first case in the benzene nucleus, and in the second in the side chain. Chloro-toluene is  $C_6H_4Cl \cdot CH_3$ , and benzyl chloride  $C_6H_5 \cdot CH_2Cl$ .

When the halogens replace hydrogen of the benzene nucleus, the products are extremely stable, and the halogen cannot readily be removed from the molecule. Thus to replace Cl in  $C_6H_5\cdot Cl$  by OH heating to  $300^\circ$  with 20 per cent aqueous NaOH is necessary. For exceptions see 2:4-dinitrochloro- and *s*-trinitrochloro-benzene. On the other hand, when the halogen replaces hydrogen atoms of a side chain (methyl or ethyl groups), the compound is extremely reactive, and closely resembles the halogen derivatives of the fatty series. In this way it is always easy to arrive at the constitution of a compound from the behaviour of its halogen atoms and from its products of oxidation. Thus a compound  $C_7H_6Cl_2$ , which yields monochloro-benzoic acid upon oxidation, must be a chloro-benzyl chloride,  $C_6H_4Cl\cdot CH_2Cl$ .

The majority of aromatic halogen derivatives, independently of the position of the halogen in the side chain or nucleus, react in dry ethereal solution (or in benzene in presence of a little dimethyl-aniline) with dry magnesium powder, yielding organo-magnesium compounds, e.g.  $C_6H_5\cdot Mg\cdot Br$ , phenyl-magnesium bromide,  $C_6H_5\cdot CH_2\cdot Mg\cdot Cl$ , benzyl-magnesium chloride, &c. These compounds—*Grignard's* compounds—are chemically extremely active, and, like the analogous aliphatic compounds (Chap. IV, H.), can be employed for the syntheses of saturated and unsaturated hydrocarbons, primary, secondary, and tertiary alcohols, thiophenols, aldehydes, ketones, acids, &c.

The *Grignard* compounds may also be used for converting a bromo-derivative into the corresponding iodo-compound, e.g.:



The boiling-points of the isomeric halogen substitution products differ but little from one another (cf. *o*-, *m*-, *p*-chloro-benzene and benzyl chloride).

The influence of the introduction of F, Cl, Br, or I in place of hydrogen on the boiling-point of a hydrocarbon is similar to that noted in the fatty series. Iodine raises the boiling-point to the greatest extent, and fluorine to the least.

The halogen derivatives may be nitrated, sulphonated, &c., in much the same manner as benzene itself.

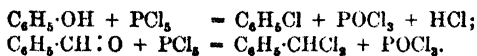
*Modes of Formation.*—1. By the action of chlorine or bromine upon aromatic hydrocarbons there are formed, according to

the conditions, either additive or substitution products, the latter class especially in presence of iodine or some other halogen carrier. The function of the halogen carrier, e.g. I, P, Fe, &c., is probably to form an additive compound with the halogen, e.g.  $\text{ICl}_3$ ,  $\text{PCl}_5$ ,  $\text{FeCl}_3$ , then to give up part or the whole of the halogen in the nascent state to the hydrocarbon, and then to be immediately converted back into the above compounds again (cf. p. 61). In many cases the rate of substitution is directly proportional to the concentration of the catalyst (*Slator*, J. C. S., 1903, 729). Iodine only substitutes directly under the conditions detailed at p. 62. From benzene most of the chlorinated derivatives up to  $\text{C}_6\text{Cl}_6$  can be obtained in succession; the last-named compound is formed with the aid of  $\text{MoCl}_5$ ,  $\text{ICl}_3$ , &c., at a somewhat high temperature. A hexabromo-benzene and a hexa-iodo-compound also exist. In the case of toluene and its homologues the halogen enters the benzene nucleus alone if the operation is performed in the cold, with the exclusion of direct sunlight or with the addition of iodine; while if the gas is led into the boiling hydrocarbon, or if the experiment is conducted in sunlight and without addition of iodine, it goes almost exclusively into the side chain, yielding  $\text{C}_6\text{H}_5\cdot\text{CH}_2\text{Cl}$ ,  $\text{C}_6\text{H}_5\cdot\text{CHCl}_2$  and  $\text{C}_6\text{H}_5\cdot\text{CCl}_3$  (*Beilstein*; *Schramm*; cf. J. C. S., 1910, 1623). Bromination of benzene and its alkyl derivatives readily takes place in presence of beryllium and water, yielding di-, tri-, and even tetra-substituted derivatives  $\text{C}_6\text{H}_4\text{R}_2 \rightarrow \text{C}_6\text{Br}_4\text{R}_2$  (*Pajeau*, C. R., 1937, 204, 1202).

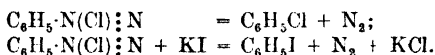
In the ordinary processes of substitution only half the halogen used enters the hydrocarbon molecule, the remainder is used up in forming halogen hydride. Working with bromine or iodine in the presence of concentrated nitric acid, *Datta* and *Chatterjee* (J. A. C. S., 1916, 2545; 1917, 435; 1919, 292) obtained good yields of bromo- and iodo-substitution products without the formation of halogen hydride.

The addition of  $\text{AlCl}_3$  to a mixture of sulphur monochloride and sulphuryl chloride forms a powerful chlorinating agent (*Silberrad*, J. C. S., 1922, 1015).

2. From compounds containing oxygen (the phenols, aromatic alcohols, aldehydes, ketones, and acids), by the action of phosphorus pentachloride or bromide:



3. From the primary amines. The amine is first converted into a diazonium salt (Chap. XXII, A.), and this is then warmed with solutions of cuprous chloride or bromide, when the corresponding chlorine or bromine compound is obtained. If the diazonium salt is warmed with potassium iodide solution, iodo-substitution products are obtained:



*Gattermann's* modification consists in transforming the amine into the diazonium chloride, bromide, or iodide, and then decomposing this with finely-divided copper powder (*Sandmeyer*, B., 1884, 1633, 2650; *Gattermann*, B., 1890, 1218):



***p*-Dibromo-benzene** is obtained, together with bromo-benzene, by bromination of benzene in presence of a little iron.

The **trichloro-benzene** which results by direct substitution has the (asymmetric) constitution 1 : 2 : 4. It may also be formed by the separation of 3HCl from  $\text{C}_6\text{H}_6\text{Cl}_6$ .

**Hexachloro- and hexabromo-benzenes** are produced by the prolonged chlorination or bromination of benzene, toluene, naphthalene, &c., and also from carbon tetrachloride and bromide; cf. p. 403. They are solids and can be distilled.

When toluene is chlorinated or brominated, as given on p. 417, the para- and ortho-compounds are formed in approximately equal quantities. *m*-Chloro-toluene is obtained from chloro-*p*-toluidine,  $\text{C}_6\text{H}_3\text{Cl}(\text{NH}_2)\text{CH}_3$  (from *p*-toluidine and Cl), according to method 3. Oxidation by  $\text{HNO}_3$ ,  $\text{CrO}_3$ , or  $\text{KMnO}_4$  converts them into the halogenated benzoic acids, but chromic acid mixture must only be used in the case of the *p*- and *m*-, and not in that of the *o*-compounds, as it completely disintegrates the latter.

**Benzyl chloride**,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\text{Cl}$  (*Cannizzaro*), is prepared by chlorinating boiling toluene, and benzyl bromide in an analogous manner; the latter can be converted into benzyl iodide by potassium iodide solution. The behaviour of these compounds shows them to be the halide esters of benzyl alcohol,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{OH}$ , from which they may be obtained by the action of halogen hydride, or of halogen derivatives of phosphorus, and into which they are transformed by prolonged boiling with water, or better, with a solution of potassium

carbonate. When boiled with potassium acetate, the chloride yields benzyl acetate, with potassium sulph-hydrate the mercaptan, and with ammonia the amine.

The compounds containing halogen in the side chain irritate the mucous membrane of the nose and eyes exceedingly, and are used as lachrymatory gases. On oxidation they yield benzoic acid. Benzyl chloride is used on the large scale for the preparation of oil of bitter almonds and also of certain dyes.

**Benzal chloride**, *Benzylidene chloride*,  $C_6H_5 \cdot CHCl_2$ , and **benzo-trichloride**,  $C_6H_5 \cdot CCl_3$ , are produced by the further chlorination of boiling toluene and also by the action of  $PCl_5$  upon the corresponding oxygen compounds, benzaldehyde,  $C_6H_5 \cdot CHO$ , benzoic acid,  $C_6H_5 \cdot CO_2H$ , and benzoyl chloride,  $C_6H_5 \cdot COCl$ . They are liquids resembling benzyl chloride, and are reconverted into the original oxygen compounds by superheating with water, and into benzoic acid by oxidizing agents.

**Chlorobromo-benzenes**,  $C_6H_4ClBr$ , **chlor-iodo-benzenes**, and other mixed derivatives also exist in large number.

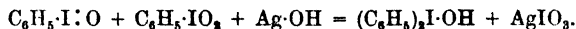
Substitution compounds of unsaturated hydrocarbons are likewise known, e.g.  **$\beta$ -bromo-styrene**,  $C_6H_5 \cdot CBr : CH_2$ ,  **$\alpha$ - or  $\omega$ -bromo-styrene**,  $C_6H_5 \cdot CH : CHBr$ , &c.

**Iodine Derivatives containing a Polyvalent Iodine Atom.**—The iodine atom attached to the nucleus may in many cases unite with other atoms, and thus exercise a higher valency. The compounds thus obtained have but few analogues in the fatty series, an example is iodoso-fumaric acid.

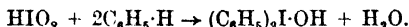
**Phenyl-iodide dichloride**,  $C_6H_5 \cdot I : Cl_2$  (*Willgerodt*, 1893), is formed as a yellow crystalline compound when dry chlorine is led into a chloroform solution of phenyl iodide. The chlorine is loosely combined, and may be removed on warming, or by the action of potassium iodide. Alkalis transform the dichloride into **iodoso-benzene**,  $C_6H_5 \cdot I : O$ , a yellow amorphous base which dissolves in acids, yielding salts, e.g. **acetate**,  $C_6H_5 \cdot I(C_2H_3O_2)_2$ , **nitrate**,  $C_6H_5 \cdot I(Q \cdot NO_2)_2$ , &c. The base decomposes when heated, oxidizes potassium iodide solution, and when kept or when distilled in steam is converted into phenyl iodide and **iodoxy-benzene**,  $C_6H_5 \cdot IO_2$ . This latter is crystalline, explodes when heated, is not basic, and resembles peroxides. It may also be prepared by oxidizing the iodoso-compound or even the iodide with *Caro's* reagent.

**Iodonium compounds** (*Hartmann* and *V. Meyer*, B., 1894,

1592), e.g. **diphenyl-iodonium iodide**,  $(\text{C}_6\text{H}_5)_2\text{I}\cdot\text{I}$ , and the corresponding **hydroxide**,  $(\text{C}_6\text{H}_5)_2\text{I}\cdot\text{OH}$ , can be obtained when a mixture of iodoso- and iodoxy-benzene is shaken with moist silver oxide:



Iodonium compounds are also formed by the action of iodic and sulphuric acids on compounds  $\text{C}_6\text{H}_5\text{X}$ , where  $\text{X} = \text{H}$ ,  $\text{Me}$ ,  $\text{Cl}$ ,  $\text{Br}$ ,  $\text{I}$  (J. C. S., 1937, 1718). The reaction may be due to iodosous acid  $\text{HIO}_2$  formed from the iodic acid:



The hydroxide which is only known in solution has strongly alkaline properties. The salts, which crystallize well, closely resemble the thallium salts. It is highly probable that the three valencies of the polyvalent iodine atom in these iodonium salts lie in the same plane, as, according to *Peters and Kipping* (J. C. S., 1902, 1350), stereo-isomerides of the form  $\text{RR}'\text{I}\cdot\text{X}$  do not appear to exist, and no resolution into optically active components can be effected.

## XX. NITRO-SUBSTITUTION PRODUCTS OF THE AROMATIC HYDROCARBONS

When benzene and its derivatives are treated with concentrated nitric acid, most of them are easily dissolved, with evolution of heat, and transformed into nitro-compounds which are precipitated on the addition of water. According to the conditions of the experiment and the nature of the compound to be nitrated, one or more nitro-groups enter the molecule (see, e.g., phenol). The nitro-groups substitute in the nucleus, and only very seldom in the side chain (cf. p. 424).

Very often fuming nitric acid or a mixture of fuming nitric and concentrated sulphuric (or fuming sulphuric) acid is used. The advantage of the addition of sulphuric acid is to keep the nitric acid from becoming too dilute. The stronger the acid and the higher the temperature, the larger the number of nitro-groups introduced. The homologues of benzene are, as a rule, nitrated more readily than benzene itself.

Anhydrous pyridinium nitrate in presence of excess of pyridine is useful for nitrating the higher hydrocarbons. (*Bull. Soc.*, 1922 (IV), **31**, 91.)

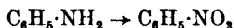
## SUMMARY

		Positions of Substituents	M.-pt.	B.-pt.	Sp. gr.
$C_6H_5 \cdot NO_2$	.. Nitro-benzene	—	+ 6°	210°	1.204
$C_6H_4(NO_2)_2$	.. <i>o</i> -Dinitro-benzene	1 : 2	117	319	—
	<i>m</i> -Dinitro-benzene	1 : 3	90	297	—
	<i>p</i> -Dinitro-benzene	1 : 4	171	—	—
$C_6H_3(NO_2)_3$	.. <i>s</i> -Trinitro-benzene	1 : 3 : 5	122	†	—
	<i>as</i> -Trinitro-benzene	1 : 2 : 4	57.5	—	—
$CH_3 \cdot C_6H_4 \cdot NO_2$	.. <i>o</i> -Nitro-toluene	*1 : 2	-10.5	222	1.168
	<i>m</i> -Nitro-toluene	1 : 3	+ 16	228	1.168
	<i>p</i> -Nitro-toluene	1 : 4	54	238	(1.123 (54°))
$CH_3 \cdot C_6H_3 \cdot (NO_2)_2$	2:4-Dinitro-toluene	1 : 2 : 4	70	†	—
	2:6-Dinitro-toluene	1 : 2 : 6	60	—	—
$CH_3 \cdot C_6H_2(NO_2)_3$	2:4:6-Trinitro-toluene	1 : 2 : 4 : 6	81	—	—
$(CH_3)_2 \cdot C_6H_3 \cdot NO_2$	.. 4-Nitro-xylene	1 : 3 : 4	+ 2	246	1.135
$(CH_3)_3 \cdot C_6H_2 \cdot NO_2$	.. Nitro-mesitylene	1 : 3 : 5 : 2	44	255	—

Nitro-compounds are also produced by the action of nitrous acid upon diazonium compounds in the presence of cuprous oxide (*Sandmeyer*, B., 1887, 1494):



and also by the oxidation of primary aromatic amines:



(*Bamberger*, B., 1893, 496). These reactions, however, are mainly of theoretical interest. They cannot, however, be prepared according to mode of formation 1 for nitro-methane (p. 104), i.e. by the action of  $AgNO_2$  on  $C_6H_5Cl$ , &c.

The nitro-compounds are, for the most part, pale-yellow liquids which distil unchanged and volatilize with water vapour; some form colourless or pale-yellow crystals; sometimes they are also of an intense yellow or red colour. Many of them explode when heated. They are heavier than water, and insoluble in it; but most of them are readily soluble in alcohol, ether, and glacial acetic acid.

The nitro-group in most aromatic nitro-compounds is firmly attached as in the case of the nitro-methanes, and is not

\* The positions of  $CH_3$  group, or groups, are always given first.

† Most of the polynitro-compounds are volatile, but decompose when heated



exchangeable for other groups. Like the latter compounds also, they are readily reduced in acid solution to the corresponding amines; in alkaline solution they are converted into azoxy-, azo-, and hydrazo-compounds (see these), and in neutral solution into hydroxylamine derivatives.

When reduced electrolytically, nitro-benzene can yield either phenyl-hydroxylamine,  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{OH}$ , which is immediately transformed into *p*-amino-phenol,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$  (Gattermann, B., 1893, 1814; 1894, 1927), or it can yield aniline. When hydrogen is passed into an alcoholic solution of nitro-benzene containing colloidal palladium, aniline is formed (cf. Chap. XLIX, A.).

**Nitro-benzene**,  $\text{C}_6\text{H}_5(\text{NO}_2)$  (Mitscherlich, 1834), is formed when a mixture of sulphuric and the calculated quantity of nitric acid is added to benzene. It is a yellow liquid with an intense odour of oil of bitter almonds, solidifies in the cold, melts at  $+5^\circ$ , and is used as a cheap scent for soaps and also for the manufacture of aniline.

**Dinitro-benzenes**,  $\text{C}_6\text{H}_4(\text{NO}_2)_2$ , are produced when benzene is boiled with fuming nitric acid; in this, as in all analogous cases, the two nitro-groups take up the meta-position to one another, very little of the *o*- and *p*-compounds being formed, and after crystallizing from alcohol, pure *m*-dinitro-benzene is obtained in long colourless needles.

The *o*-compound crystallizes in plates and the *p*-compound in needles, both being colourless; they are prepared indirectly by eliminating  $\text{NH}_2$  from the corresponding di-nitranilines.

When reduced, they yield first the three nitranilines, and then the phenylene-diamines (Chap. XXI, E.).

*o*-Dinitro-benzene exchanges a nitro-group for hydroxyl when boiled with caustic soda, and for an amino-group when acted on by ammonia, yielding *o*-nitro-phenol,  $\text{C}_6\text{H}_4(\text{NO}_2)(\text{OH})$ , and *o*-nitraniline,  $\text{C}_6\text{H}_4(\text{NO}_2)(\text{NH}_2)$ , respectively. These reactions appear to be characteristic of all compounds containing two nitro-groups in ortho-positions. The *m*-compound is oxidizable by  $\text{K}_3\text{FeC}_6\text{N}_6$  to  $\alpha$ - and  $\beta$ -dinitro-phenol.

***s*-Trinitro-benzene** crystallizes in colourless plates, melts at  $122^\circ$ , and forms additive compounds with aromatic hydrocarbons, phenols, and especially with aromatic bases, e.g. aniline, naphthylamine. Most of these are well-defined crystalline compounds of red, reddish-brown, or black colour, and are readily resolved into their components by warm mineral acids.

**Nitro-toluenes**,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2$ .—When toluene is nitrated, the *p*- and *o*-compounds, with very little *m*-compound, are formed. The first is solid, crystallizing in large prisms, and the second liquid, the latter being used as a perfume under the name of "oil of mirbane"; both are employed in the colour industry. *m*-Nitro-toluene can be prepared indirectly from *m*-nitro-*p*-toluidine,  $\text{C}_6\text{H}_3(\text{CH}_3)(\text{NO}_2)(\text{NH}_2)$ , by the elimination of the amino-group (Chap. XXII, A.). Further nitration gives rise to:

**Dinitro-toluenes**,  $\text{CH}_3\cdot\text{C}_6\text{H}_3(\text{NO}_2)_2$ , of the constitution  $\text{CH}_3:\text{NO}_2:\text{NO}_2 = 1:2:4$  and  $1:2:6$ , the two nitro-groups being again in the *m*-position to one another in both cases, and finally to *s*-trinitro-toluene, "T.N.T.", an important high explosive. With ammonium nitrate it forms *amatol*.

Most of these nitro-compounds are of great technical importance, on account of the readiness with which they are reduced to amines.

Several polynitro-compounds are used as "artificial musk" odours: 1. **Xylene musk** from *m*-xylene which with tertiary butyl chloride by the *Friedel-Crafts* reaction yields 1:3-dimethyl-5-tert-butyl-benzene, and this on nitration gives the musk 1:3-dimethyl-5-tert-butyl-2:4:6-trinitro-benzene  $\text{C}_4\text{H}_9\cdot\text{C}_6\text{Me}_2(\text{NO}_2)_3$ . 2. **Ambretta musk**, obtained in a similar manner from *m*-cresol, is 1-methyl-2-tert-butyl-5-methoxy-3:6-dinitrobenzene. 3. **Musk ketone**, with a civet odour obtained from *m*-xylene by introducing the butyl group, then the acetyl group, and finally nitrating is 1:3-dimethyl-5-tert-butyl-2-acetyl-4:6-dinitrobenzene.

**Chloro- and Bromo-nitro-benzenes**.—When chloro- or bromo-benzene is nitrated, *p*-chloro- (or bromo-) nitro-benzene is formed, together with smaller quantities of the *o*-compounds. The *m*-compounds must be prepared indirectly by replacing an amino-group in *m*-nitraniline by halogen. The *p*-derivatives have a higher melting-point than their isomers, and the *m*-compounds for the most part a higher one than the *o*-derivatives, this law frequently repeating itself in other cases also. The *p*-derivatives are usually also less soluble in alcohol. The *o*- and *p*-compounds, but not the *m*-, exchange halogen for hydroxyl when boiled with potash, and for the amino-group when heated with ammonia.

In *s*-trinitro-chloro-benzene,  $\text{C}_6\text{H}_2(\text{NO}_2)_3\text{Cl}$ , and in 1-chloro-2:4-dinitro-benzene the chlorine atoms have been rendered so

readily exchangeable, that the compounds behave as alkyl chlorides, or even as acid chlorides; hence the name "picryl chloride", the chloride of picric acid (Chap. XXIV, A1), for the former compound.

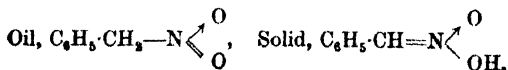
*o*-, *m*-, and *p*-**Nitro-styrenes**,  $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{CH}_2$ , can be prepared by indirect methods.  $\mu$ -**Nitro-styrene**,  $\text{C}_6\text{H}_5 \cdot \text{CH} : \text{CH} \cdot \text{NO}_2$ , which is formed by the action of nitrous acid on styrene, contains the nitro-group in the side chain, since it can be prepared from benzaldehyde and nitro-methane by means of zinc chloride:



*o*-**Nitro-phenyl-acetylene**,  $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C} : \text{CH}$ , formed when *o*-nitro-phenyl-propionic acid is boiled with water, crystallizes in colourless needles.

**Phenyl-nitro-methane**,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{NO}_2$ , isomeric with the nitro-toluenes, is the most typical of the aromatic nitro-derivatives with a nitro-group in the side chain. It is formed by the action of nitric acid (D 1·12) on toluene under pressure, and also by the action of benzyl halides on silver nitrite (cf. Nitro-methane). It is a true nitro-derivative, and not an alkyl nitrite (benzyl nitrite,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{O} \cdot \text{N} : \text{O}$ ), as it is not readily hydrolysed, and when reduced yields benzylamine,  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{NH}_2$ . It exists in two distinct modifications, which are readily transformed into each other. As generally prepared, it is a colourless liquid with a characteristic odour, boils at  $225^\circ$ – $227^\circ$ , and dissolves to a certain extent in water, yielding a solution which does not give a coloration with ferric chloride. The second modification, which is a crystalline solid melting at  $84^\circ$ , is formed when the sodium derivative obtained from the oily compound is decomposed in the cold by hydrochloric acid. The solid modification is relatively unstable, and gradually passes over into the oily form. The solid is probably a hydroxy-compound, since (a) its aqueous solution gives a red-brown coloration with ferric chloride, (b) it reacts with phenyl-carbimide, (c) it reacts with  $\text{PCl}_5$ , and (d) with benzoyl chloride it gives dibenzhydroxamic acid,  $\text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{NH} \cdot \text{O} \cdot \text{COC}_6\text{H}_5$  (from  $\text{C}_6\text{H}_5 \cdot \text{CH} : \text{N}(\text{O} \cdot \text{COC}_6\text{H}_5) : \text{O}$ ).

The two forms are thus:



The tendency to form isonitro-compounds is also shown by certain aliphatic nitro-compounds. (Cf. Absorption Spectra, Chap. LXXI, D.)

The oily compound, although it gives rise to a sodium salt, is, strictly speaking, not an acid; it is what is termed a *pseudo-acid*, and before it yields a sodium salt it undergoes intramolecular rearrangement, yielding the true acid—the isonitro-compound. When the sodium salt is treated with a mineral acid, the isonitro-compound, or true acid, is first formed; but as this is unstable, it gradually changes over into the true nitro- or pseudo-acid form. Numerous examples of pseudo-acids, i.e. compounds which on formation of metallic salts undergo intramolecular rearrangement so that the original substance has a structure different from that of the salt, have been investigated by *Hantzsch* (B., 1899, 575; 1902, 210, 226, 1001; 1906, 139, 1073, &c.), who describes the following as some of the most characteristic criteria of pseudo-acids (cf. also Chap. LXXI, J.):

1. The compound is a pseudo-acid if it *gradually* neutralizes an alkali. The pseudo-acid, as such, does not neutralize the base, but is first transformed into the isomeric true acid, which then neutralizes the alkali. If the transformation is slow, then the process of neutralization is also slow. Similarly, if when a solution of a salt of the acid is decomposed by an equivalent quantity of a mineral acid, the electrical conductivity gradually falls to that required for the metallic salt of the mineral acid, it indicates that the acid is a pseudo-acid, e.g. barium isonitro-methane + HCl give isonitro-methane + BaCl<sub>2</sub>, and then nitro-methane + BaCl<sub>2</sub>. Isonitro-methane is a fairly strong acid, and hence is dissociated to an appreciable extent; as it becomes transformed into nitro-methane (the pseudo-acid) the conductivity will diminish, as nitro-methane is an extremely feeble acid—scarcely ionized.

2. If the original compound is extremely feebly acidic, and yet yields a sodium derivative which dissolves in water yielding a practically neutral solution, then the compound must be a pseudo-acid. It is a well-known fact that only sodium salts derived from comparatively strong acids, e.g. NaCl, Na<sub>2</sub>SO<sub>4</sub>, NaI, &c., dissolve in water to neutral solutions, i.e. are not hydrolysed by water. The sodium salts derived from feeble acids are always appreciably hydrolysed, e.g. Na<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>·COONa, &c. Hence if the sodium salt is not hydrolysed to

an appreciable extent, the salt must be derived from a strong acid (the true acid), and the non- or feebly acidic compound must be the pseudo-acid.

3. If the compound in question will not yield a salt with ammonia in an anhydrous solvent, e.g. dry benzene, but will do so in the presence of water, e.g. in moist ether, then the substance is a pseudo-acid. The formation of a salt in dry ether does not necessarily indicate that the substance is a true acid.

4. If the compound dissolves in water or in other dissociating (ionizing) media to a colourless solution, but yields a coloured solid salt or coloured ions when dissolved in alkalis, it is a pseudo-acid.

5. An abnormally high temperature coefficient for the electrical conductivity and an increase in the coefficient with rise of temperature are further indications of pseudo-acids.

Nitro-methane, bromo-nitro-methane, dibromo-nitro-methane, nitro-ethane, phenyl-nitro-methane, phenyl-bromo-nitro-methane, in addition to numerous other organic compounds, e.g. cyanuric acid, react as pseudo-acids.

#### NITROSO-DERIVATIVES OF THE HYDROCARBONS

**Nitroso-benzene**,  $C_6H_5 \cdot N:O$ , an aromatic compound which contains the nitroso-group,  $\cdot N:O$ , in place of a benzene hydrogen atom, is produced by the action of nitrosyl chloride,  $NO \cdot Cl$ , upon mercury diphenyl dissolved in benzene; it is also obtained by the oxidation of diazo-benzene with alkaline permanganate, and most readily by the oxidation of phenyl-hydroxylamine with chromic acid or ferric chloride. Its formation by the oxidation of the amine with *Caro's* reagent (ammonium persulphate and sulphuric acid) affords a simple method of replacing  $NH_2$  by  $NO_2$  as the nitroso- is readily oxidized to the nitro-group. It forms colourless plates, melts at  $68^\circ$ , yields green solutions, and possesses a powerful odour similar to that of cyanic acid. The solid is dimeric but dissociates in solution, and an ortho-group tends to retard dissociation. When reduced it yields aniline. It readily condenses with different compounds, e.g. with aniline in the presence of acetic acid to azo-benzene:



and with phenyl-hydroxylamine to azoxy-benzene.

**Nitroso-derivatives of tertiary amines** are obtained directly by the action of nitrous acid upon the latter (See Nitroso-dimethyl-aniline,  $\text{NO}\cdot\text{C}_6\text{H}_4\cdot\text{N}(\text{CH}_3)_2$ , Chap. XXI, C.)

## XXI. AMINO-DERIVATIVES OR ARYLAMINES \*

(See Table, following page)

Aniline, the simplest of the aromatic bases, may be regarded (1) as benzene in which a hydrogen atom is replaced by the amino-group ("amino-benzene"), or (2) as ammonia in which a hydrogen atom is replaced by phenyl,  $\text{C}_6\text{H}_5\cdot$ , ("phenyl-amine"). According to the former view, amino-compounds can be derived from all the benzene hydrocarbons, and not only monamines (containing  $\text{NH}_2$ ), but also diamines ( $2\text{NH}_2$ ), triamines, &c.; according to the latter, the phenyl group may enter anew with the formation of secondary or tertiary amines. Secondary and tertiary amines, and even quaternary ammonium compounds, may also result from the entrance of alkyl-radicals into the above monamines, diamines, &c. Amines are also known in which the  $\text{NH}_2$  group is attached to a carbon atom of a side chain, e.g.  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{NH}_2$ . These compounds differ in many respects from aniline and its homologues.

An extraordinarily large number of aromatic bases are thus theoretically possible, and also actually known. In certain respects they closely resemble the aliphatic amines, e.g. they form salts with acids, e.g.  $\text{C}_6\text{H}_5\text{NH}_2$ ,  $\text{HCl}$ , and complex salts, e.g. platinichlorides and aurichlorides,  $2\text{C}_6\text{H}_5\text{NH}_2$ ,  $\text{H}_2\text{PtCl}_6$  and  $\text{C}_6\text{H}_5\text{NH}_2$ ,  $\text{HAuCl}_4$ ; they possess a basic odour, give rise to white clouds with volatile acids, and distil for the most part unchanged, &c. As a rule, however, they are weaker bases than the aliphatic amines, since the phenyl group,  $\text{C}_6\text{H}_5$ , pos-

\* To distinguish between monovalent alcoholic or hydrocarbon radicals of the fatty and aromatic series the following system has been suggested: The term alkyl group comprises all such monovalent radicals whether of the aliphatic series, e.g.  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ , or of the aromatic, e.g.  $\text{C}_6\text{H}_5$ ,  $\text{CH}_2\cdot\text{C}_6\text{H}_4$ ,  $\text{C}_6\text{H}_4\cdot\text{CH}_2$ , &c. The purely aliphatic alkyl radicals are termed aliphyl groups, and the aromatic, aryl (*Vorländer*, J. pr. [2], 59, 247). Thus aniline is often spoken of as a type of the arylamines.

sesses a negative (acylous) character, and not—like the aliphyl radicals—a positive (basylous); thus the salts of diphenylamine are decomposed even by water, and triphenylamine no longer possesses basic properties, while dimethyl-aniline has a strongly-marked basic character.

The diamines have a more strongly basic character than the monamines, and are more readily soluble in water.

### ANILINE AND ITS HOMOLOGUES

Formula	Name	Positions of Substituents NH <sub>2</sub> in 1	M.-pt.	B.-pt.	M.-pt. of Acetyl Derivative
C <sub>6</sub> H <sub>5</sub> ·NH <sub>2</sub> ..	Aniline ..	—	— 8°	184°	114°
C <sub>6</sub> H <sub>4</sub> Me·NH <sub>2</sub>	<i>o</i> -Toluidine ..	1 : 2	liq.	199	109
	<i>m</i> -Toluidine ..	1 : 3	liq.	199	66
	<i>p</i> -Toluidine ..	1 : 4	43	200	145
C <sub>6</sub> H <sub>3</sub> Me <sub>2</sub> ·NH <sub>2</sub>	<i>adj.</i> - <i>o</i> -xylidene	1 : 2 : 3	liq.	223	134
	<i>unsym.</i> - <i>o</i> -xylidene	1 : 3 : 4	49	224	99
	<i>adj.</i> - <i>m</i> -xylidene	1 : 2 : 6	liq.	215	177
	<i>p</i> -xylidene ..	1 : 2 : 5	15·5	213	139
C <sub>6</sub> H <sub>2</sub> Me <sub>3</sub> ·NH <sub>2</sub>	Mesidine ..	1 : 2 : 4 : 6	liq.	229	216
	Pseudo-cumidine	1 : 2 : 4 : 5	68	234	161
C <sub>6</sub> H <sub>5</sub> ·NHMe	Methyl-aniline	—	—	194	101
C <sub>6</sub> H <sub>3</sub> ·NMe <sub>2</sub> ..	Dimethyl-aniline	—	—	193	163*
C <sub>6</sub> H <sub>5</sub> ·NEt ..	Ethyl-aniline ..	—	—	206	53
C <sub>6</sub> H <sub>5</sub> ·NEt <sub>2</sub> ..	Diethyl-aniline	—	—	216	142*
C <sub>6</sub> H <sub>5</sub> ·CH <sub>2</sub> ·NH <sub>2</sub>	Benzylamine ..	—	—	184	61

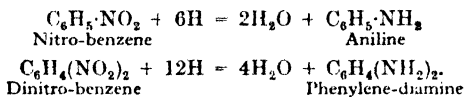
\* m.-pt. of picrate.

### A. Primary Monamines

*Isomers.*—The isomerism of the aromatic is in part analogous to that of the fatty amines (p. 115), e.g. dimethyl-aniline is isomeric with the methyl-toluidines and the xylidines. Cases of isomerism are also caused by the amino-group being present in the benzene nucleus in the one case, and in the side chain in the other. Finally, position isomerides are frequently met with, e.g. *o*-, *m*-, and *p*-toluidines, CH<sub>3</sub>·C<sub>6</sub>H<sub>4</sub>·NH<sub>2</sub>.

*Constitution.*—As already seen at pp. 115 *et seq.*, amines are very easy to characterize as primary, secondary, &c. In addition, their modes of formation, and also their behaviour, show whether the amino-group of a primary amine is present in the benzene nucleus or in the side chain.

*Modes of Formation.*—1. The most important mode of preparation of the primary arylamines, whether mono- or di-, &c., is the reduction of the corresponding nitro-compounds:



The usual method of introducing an amino-group into a benzene hydrocarbon is to first nitrate and then reduce. An interesting direct method for the introduction of the  $\text{NH}_2$  group is by the action of ferric or aluminic chloride on a mixture of the hydrocarbon and hydroxylamine hydrochloride (B., 1901, 1778):



The reduction of nitro- to amino-compounds takes place most readily in acid solution, e.g. by the gradual addition of the former to a warm mixture of tin or stannous chloride and hydrochloric acid. On a manufacturing scale, iron and a limited amount of hydrochloric acid are used (*Béchamp*), also frequently zinc dust and hydrochloric or acetic acid. Ammonium sulphide (*Zinin*), ferrous sulphate, and baryta water, &c., also effect the reduction. (See Aniline and Chap. XLVII on Reduction.) With alkaline reducing agents the products are usually azoxy-, azo-, or hydrazo-compounds (cf. Chap. XXII, C.).

Aniline and its homologues may also be obtained by the electrolytic reduction of nitro-compounds.

Ammonium sulphide acts more mildly than tin and hydrochloric acid, and is therefore of special value for the partial reduction of dinitro-compounds (see Nitraniline). An alcoholic solution of stannous chloride containing hydrochloric acid may also be used for this purpose (B., 1886, 2161).

Amines are also formed when nitroso-compounds and aryl-hydroxylamines are reduced.

2. By heating phenols with the compound of zinc chloride and ammonia, or of calcium chloride and ammonia, to  $300^\circ$  (*Merz*), secondary amines being formed at the same time:



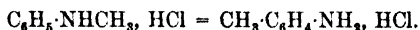


This reaction proceeds more easily in the presence of negative groups, e.g. with the nitro-phenols (B., 1886, 1749).

3. By distilling amino-acids with lime, sometimes by merely heating them alone:



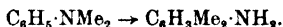
4. When the hydrochlorides of secondary and tertiary amines of the type of mono- and di-methyl-aniline are heated in sealed tubes, the methyl groups wander from the nitrogen atom to a carbon atom of the benzene nucleus, e.g. methyl-aniline hydrochloride at 335° yields toluidine hydrochloride:



The methyl groups invariably take up the *o*- or *p*-, and not the *m*-position, with respect to the amino-group.

Similarly, the final product obtained by heating phenyl-trimethylammonium iodide,  $\text{C}_6\text{H}_5\cdot\text{NMe}_3\text{I}$ , is mesidine hydriodide,  $\text{C}_6\text{H}_2\text{Me}_3\cdot\text{NH}_2[\text{NH}_2:\text{Me}_3 = 1:2:4:6^*]$ . Diphenylamine hydrochloride does not behave in a similar manner.

This reaction, often known as the *Hofmann* reaction, is of considerable service in obtaining the higher homologues of aniline from aniline, toluidine, &c. Aniline is readily converted into dimethyl-aniline, and when the hydrochloride of this is heated to about 300° the methyl groups wander from the side chain into the nucleus (cf. Chap. XXXVIII):



5. Primary amines can be obtained from acid amides by *Hofmann's* reaction (cf. p. 212), viz. treatment with bromine and alkali, or from acid azides,  $\text{R}\cdot\text{CO}\cdot\text{N}_3$ . When boiled with alcohol the azide yields nitrogen and, by molecular rearrangement, a urethane,  $\text{R}\cdot\text{NH}\cdot\text{CO}\cdot\text{OEt}$ , and this on hydrolysis gives a primary amine,  $\text{RNH}_2$ .

6. The aromatic amines cannot, as a rule, be obtained by heating chloro-benzene, &c., with ammonia unless there is a nitro-group in the ortho- (or para-) position with respect to the halogen. Benzylamine, however, and all analogously constituted bases, which contain the  $\text{NH}_2$  group in the side chain, can be obtained by the methods employed for the preparation of aliphatic amines. Thus benzylamine is formed by

\* The numbers 1:2:4:6 indicate the relative positions of the amino- and three methyl-radicals in the benzene ring.

the action of ammonia, or better, of acetamide upon benzyl chloride (the latter method gives acetyl-benzylamine, which can be readily hydrolysed).

*Properties.*—The primary monamines are either liquid or solid crystalline bases. They are colourless when pure, but readily become brown when exposed to the air, largely owing to the presence of small amounts of impurities, and possess a weakly basic though not disagreeable odour. Aniline is somewhat soluble in water (1 : 31), its homologues less so.

*Behaviour.*—1. With acids most of them form crystalline salts, the majority of which are readily soluble in water. They do not, however, unite with very weak acids, such as carbonic, and they are therefore separated from their salts in the free state by sodium carbonate, and in some cases even by sodium acetate (when no acetates exist). The arylamines are weaker bases than ammonia, and the introduction of Cl or NO<sub>2</sub> into the ring depresses the basic function still further (*Farmer and Warth*, J. C. S., 1904, 1713; *Arnall*, 1920, 837). The crystalline **picrates** are often used for characterizing particular amines. They yield sparingly soluble complex salts, such as **platinichlorides**, (C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub>)<sub>2</sub>, H<sub>2</sub>PtCl<sub>6</sub>, **auri-chlorides**, C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub>, HAuCl<sub>4</sub>, and similar compounds with stannous, stannic, and zinc chlorides.

All salts of the bases are readily decomposed by strong alkalis, and the free bases are regenerated. Even in aqueous solution the salts are largely split up into free acid and free base; the result is that the strength of a solution of aniline hydrochloride may be determined by titrating the hydrochloric acid present by standard alkali hydroxide, using phenolphthaleïn as indicator. This is not due to the fact that the salt is completely hydrolysed in aqueous solution; in reality there is a state of equilibrium represented by the equation:



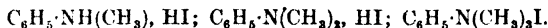
and as the HCl is neutralized by the addition of alkali, more of the aniline salt is decomposed in order to restore the equilibrium. This continues until the whole of the salt is decomposed, and the HCl neutralized by the alkali.

The amines also form additive compounds with numerous metallic salts, e.g. 2C<sub>6</sub>H<sub>7</sub>N + ZnCl<sub>2</sub>, 2C<sub>6</sub>H<sub>7</sub>N + HgCl<sub>2</sub>, &c.

2. When aniline is heated with potassium or sodium, the hydrogen is replaced by metal with formation of the compounds

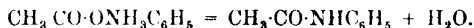
$C_6H_5NHK$  and  $C_6H_5NK_2$ . These yield di- and tri-phenylamine with bromobenzene, and decompose immediately with water.

3. The primary arylamines react with methyl iodide, benzyl chloride, &c., yielding secondary, tertiary, and even quaternary salts:

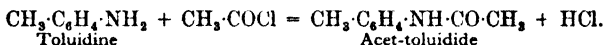


The secondary and tertiary bases can be liberated from their hydriodides by soda, but moist oxide of silver must be used in the case of the ammonium bases (see p. 119).

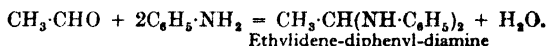
4. Just as the ammonium salts of acids can eliminate water, yielding amides, so the aniline salts can yield **anilides**, e.g. aniline acetate gives acetanilide:



These anilides may be looked upon either as acylated amines or as phenylated amides as represented in the formula  $CH_3 \cdot CO \cdot NH \cdot C_6H_5$ . They are in every respect analogous in their chemical behaviour to the ordinary amides, especially to the alkylated amides (p. 210), being hydrolysed to the acid and aniline by alkalis, and being formed by analogous methods, e.g. by heating the acid, or better, its anhydride or chloride, with the amine in question, thus:



5. Aliphatic aldehydes react with the primary bases, with elimination of water, thus:



Aromatic aldehydes, however, react as follows:



In this case an additive compound appears to be first formed,  $C_6H_5 \cdot CH(OH) \cdot NH \cdot C_6H_5$ , and this loses water, yielding benzylidene aniline,  $C_6H_5 \cdot CH : N \cdot C_6H_5$ , an example of a **Schiff's Base** or **Azomethine**.

Products of this type can also be obtained with fatty aldehydes, but they polymerize readily.

6. When warmed with chloroform and alcoholic potash, the primary bases, like those of the fatty series, yield **isonitriles** of stupefying odour. When they are warmed with carbon

disulphide, **thio-ureas** are formed, and from the latter **isothiocyanates (mustard oils)** by treatment with phosphoric acid (cf. pp. 312 and 333).

7. Bromine and chlorine, especially in the form of sodium hypochlorite or hypobromite, react with amines, forming substituted derivatives of the type  $C_6H_5 \cdot NHBr$ , in which the halogen is attached to nitrogen. These compounds are extremely unstable, can only be kept at low temperatures, and the halogen atom readily passes from the side chain into the benzene nucleus,  $C_6H_5 \cdot NHBr \rightarrow C_6H_4Br \cdot NH_2$ , usually into the *para*-position (*Chattaway and Orton*, J. C. S., 1899, 1046; 1900, 134, 152, 789, 797; also Chap. XXXVIII).

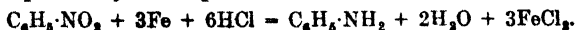
8. Nitrous acid converts the primary aromatic amines in acid solution into diazonium salts (Chap. XXII, A., I.), and in the absence of acids into diazo-amino-compounds (Chap. XXII, B.). For discussion of action of nitrous acid on primary and secondary amines see *Oddo*, G., 1914, **44**, ii, 209.

9. The oxidation products of the primary bases vary with the conditions, e.g. azo-benzene, nitroso-benzene, nitro-benzene, *p*-amino-phenol, phenols, quinones, azo-compounds, aniline black, &c.

10. The bases which contain the amino-group in the side chain possess, in contradistinction to the purely aromatic amines, the character of the amines of the fatty series, and cannot, therefore, be readily diazotized as they tend to form the corresponding alcohol.

**Aniline, amino-benzene, Phenylamine**,  $C_6H_5 \cdot NH_2$ , was first obtained in 1826 by *Unverdorben* from the dry distillation of indigo, and termed by him "crystalline"; then *Runge* found it in coal-tar in 1834, and called it "cyanol". In 1841 *Fritzsche* prepared it by distilling indigo with potash, and gave it the name of aniline; while in 1842 *Zinin* obtained it by the reduction of nitro-benzene, and called it "benzidam". It was accurately investigated by *A. W. Hofmann* in 1843, and he was able to show that all the above products are identical.

*Preparation*.—Since 1864 aniline has been prepared on a manufacturing scale by reducing nitro-benzene with iron filings and a regulated quantity of hydrochloric acid, and distilling with steam after the addition of lime. The amount of hydrochloric acid actually employed is only about  $\frac{1}{10}$  of that required by the equation:



This is probably due to the fact that the ferrous chloride is hydrolysed to the hydroxide and free HCl; this latter then reacts with the iron and produces reduction of more nitrobenzene with formation of aniline and ferrous chloride, which is again hydrolysed, and thus the reaction becomes continuous (*Raikow*, *Z. Ang. Chem.*, 1916, **29**, i, 196, 239). It is a colourless, oily, strongly refracting liquid of peculiar odour, which quickly turns yellow or brown in the air, and is finally converted into a resin. It dissolves in 31 parts of water, has no action upon litmus, and is a weaker base than ammonia, although it can displace the latter at higher temperatures. It is poisonous, burns with a smoky flame, and is a good solvent for many compounds which are otherwise not readily dissolved, e.g. indigo and sulphur. Aqueous solutions of the salts have a distinct acid reaction.

The *behaviour* of aniline has been investigated with the utmost care. Oxidation in alkaline solution leads to azobenzene, while arsenic acid produces chiefly violaniline, a violet colouring-matter. A solution of free aniline is temporarily coloured violet by one of bleaching-powder, this reaction being an extremely delicate one. A solution in concentrated  $\text{H}_2\text{SO}_4$  is first coloured red and then blue by a small grain of potassium dichromate. A solution of  $\text{K}_2\text{Cr}_2\text{O}_7$  produces in an acid solution of aniline sulphate a dark-green and then a black precipitate of aniline black and ultimately quinone,  $\text{C}_6\text{H}_4\text{O}_2$ . A mixture of aniline and toluidine may be oxidized to magenta, mauveine, &c., and a mixture of aniline and *p*-diamines to safranines (see these). When reduced catalytically, aniline yields **amino-cyclo-hexane**, boiling at  $134^\circ$ .

**Salts.**—**Aniline hydrochloride**,  $\text{C}_6\text{H}_5\cdot\text{NH}_2$ , HCl, forms large colourless plates which become greenish-grey in the air, and **aniline sulphate**,  $(\text{C}_6\text{H}_7\text{N})_2$ ,  $\text{H}_2\text{SO}_4$ , beautiful white plates, sparingly soluble in water. The **platini-chloride**,  $(\text{C}_6\text{H}_7\text{N})_2$ ,  $\text{H}_2\text{PtCl}_6$ , crystallizes in yellow plates, which are sparingly soluble.

**Substitution Products—Halogen Derivatives.**—The introduction of the  $\text{NH}_2$  group—or the OH group—into the nucleus facilitates halogenation, e.g. chlorine and bromine immediately yield *s*-tri-chloro- or -bromo-derivatives, and iodine produces mono-iodoaniline. In the chlorination of aniline it is necessary to use a solvent free from water (e.g. chloroform or glacial acetic acid), otherwise oxidation and not

substitution occurs. In bromination the simplest method is to aspirate air saturated with bromine vapour through an acid solution of aniline. In all these reactions the halogen probably first substitutes H of the  $\text{NH}_2$  group (see p. 433). In the preparation of **monochlor-aniline**, the aniline must be "protected" by using it in the form of its acetyl derivative, **acetanilide**. When this is suspended in water, it is mostly transformed by chlorine into **p-chlor-acetanilide**, which readily yields **p-chlor-aniline** on hydrolysis; the latter forms colourless crystals, m.-pt.  $71^\circ$ , b.-pt.  $231^\circ$ . The *o*- and *m*-compounds, which are both liquid, are prepared indirectly, e.g. by the reduction of *o*- or *m*-chloro-nitro-benzene.

The chlorine atoms weaken the basic functions so that **s-trichlor-aniline**,  $\text{C}_6\text{H}_2\text{Cl}_3(\text{NH}_2)$  (crystals, volatile without decomposition), no longer combines with acids in presence of water. *o*- and *p*-Chlor-anilines are only capable of taking up two more atoms of chlorine with the formation of trichlor-aniline:  $[\text{NH}_2:\text{Cl}:\text{Cl}:\text{Cl} = 1.2.4.6]$ ; *m*-chlor-aniline, on the other hand, can be further chlorinated to **tetra-** and **penta-chlor-aniline**.

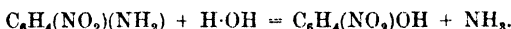
The bromo-derivatives of aniline closely resemble the chlor-anilines, and may be prepared by similar methods. The best-known compound is **s-tribrom-aniline**, which is formed by the action of bromine water on a solution of aniline hydrochloride. It crystallizes from alcohol in needles, and melts at  $119^\circ$ .

As an example of the methods sometimes employed for the preparation of halogen derivatives may be cited the preparation of 2:6-dibrom-aniline from sulphanilic acid, 1-amino-benzene-4-sulphonic acid. When carefully brominated, this yields the 2:6-dibromo-derivative; and when this is superheated with steam at  $170^\circ$  the sulphonic acid group is removed, and 2:6-dibrom-aniline, melting at  $84^\circ$ , is formed.

**Nitranilines.**—Aniline is likewise attacked far more violently than benzene by concentrated nitric acid, and therefore when it is wished to prepare the mono-nitro-compounds, the aniline must again be "protected", either by using its acetyl compound, or by nitrating in presence of excess of concentrated sulphuric acid. In the latter case all three nitranilines result, the *m*-compound preponderating. When acetanilide is nitrated, **p-nitracetanilide**,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ , and a little of the *o*-compound, are formed, and both are readily hydrolysed by potash or hydrochloric acid.

The nitranilines are further obtained by the partial reduction of the corresponding dinitro-benzenes, e.g. by means of ammonium sulphide; this is the method usually employed for the preparation of *m*-nitraniline. (For mechanism of the reaction see *Cohen and M'Candlish*, J. C. S., 1905, 1257.)

The *o*- and *p*-compounds are also formed when *o*- and *p*- $\text{C}_6\text{H}_4\text{Cl}\cdot\text{NO}_2$ ,  $\text{C}_6\text{H}_4\text{Br}\cdot\text{NO}_2$ ,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2$ , or  $\text{OEt}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2$  are heated with ammonia at  $180^\circ$  in autoclaves, and the *o*- and *p*-nitranilines are converted into nitro-phenols when boiled with alkalis, the former more easily than the latter, thus:



These are all further examples of the remarkable influence of nitro-groups on other substituents, e.g. Cl, Br, OH,  $\text{NH}_2$ , &c., in the *o*- and *p*-, but not in the *m*-position (cf. *Picryl Chloride and Picramide*, p. 480, and Chap. XXXVI).

The three nitranilines crystallize in yellow needles or prisms, and are readily soluble in alcohol, but only very slightly in water. They melt respectively at  $72^\circ$ ,  $115^\circ$ ,  $145^\circ$ , and their **acetyl** derivatives at  $93^\circ$ ,  $154^\circ$ , and  $207^\circ$ . The *o*- and *m*-compounds are volatile with steam, but not *p*-nitraniline. When reduced, they yield phenylene-diamines.

**Di- and trinitranilines**,  $\text{C}_6\text{H}_3(\text{NO}_2)_2(\text{NH}_2)$  and  $s\text{-C}_6\text{H}_2(\text{NO}_2)_3(\text{NH}_2)$ , are also known; the latter, which is termed **picramide**, and which crystallizes in yellow needles, m.-pt.  $188^\circ$ , comports itself as the amide of picric acid, since it is readily transformed into the latter compound on hydrolysis.

(For alkyl derivatives see under Secondary and Tertiary Monamines.)

**Homologues of Aniline.**—Of the three **toluidines**,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$ , the *o*- and *p*-compounds are obtained by the reduction of the corresponding nitro-compounds. The *o*- is liquid and the *p*- solid. ***m*-Toluidine**, which is liquid, may be prepared from *m*-nitro-toluene or *m*-nitro-benzaldehyde (cf. B., 1882, 2009).

The boiling-points of the three isomeric toluidines are almost identical, but the melting-points of their acetyl compounds differ widely (see table, p. 428); these are, therefore, of value for the characterization of the bases. *o*-Toluidine is coloured violet by a solution of bleaching-powder, and blue by sulphuric and nitrous acids and also by ferric chloride, but not *p*-toluidine. For their conversion into magenta see Triphenyl-methane

dyes (Chap. XXX). If during oxidation the amino-group be protected by the introduction of acetyl, the methyl radical can be oxidized to carboxyl and an acetyl derivative of amino-benzoic acid obtained. When oxidized with  $\text{KMnO}_4$ , the amino-compounds are transformed into azo-compounds.

## B. Secondary Monamines

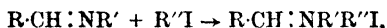
These form two distinct groups, the diarylamines, e.g.  $\text{NHPh}_2$  and the aliphylarylamines, e.g.  $\text{NHPhMe}$ .

*Modes of Formation.*—1. Mixed secondary amines are formed when the arylamines are heated with aliphyl iodides (*Hofmann*) (see p. 116), or with the alcohol and a condensing agent, e.g.  $\text{H}_2\text{SO}_4$ , under pressure. The product is usually a mixture of primary, secondary and tertiary bases, but by using an excess of the arylamine the product is the secondary base with unaltered primary, which can be removed by precipitation with zinc chloride (*Hickinbottom*, J. C. S., 1930, 992; 1933, 446. For another method of separation cf. p. 469).

A secondary base free from tertiary is formed by the action of an aliphyl iodide on the sodium derivative of an acylated arylamine, e.g.  $\text{C}_6\text{H}_5\cdot\text{NNa}\cdot\text{CO}\cdot\text{CH}_3$  or  $\text{C}_6\text{H}_5\cdot\text{NNa}\cdot\text{SO}_3\cdot\text{C}_6\text{H}_5$  and subsequent hydrolysis (B., 1877, 328; 1888, 1107).

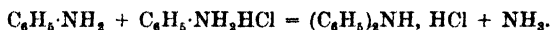
2. A convenient method is the reduction of the primary amine and an aldehyde in an alkaline medium, e.g. zinc and caustic soda. Aniline and formaldehyde yield methylaniline (*Morgan*, 1917).

3. An azomethine (p. 432) from an arylamine and aldehyde unites with an aliphyl iodide:



which yields secondary base and aldehyde on hydrolysis (A., 1913, 395, 362; J. C. S., 1916, 1033).

4. The diarylamines are formed when the primary arylamines are heated with their hydrochlorides at  $200^\circ$ :



Two different aryl radicals may be introduced, e.g.  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$ , phenyl-tolylamine.

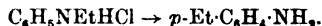
5. The usual method is the condensation of an arylamine with a halogenated benzene in the presence of a copper powder



with a little  $K_2CO_3$  (Goldberg, B., 1906, 1691; 1907, 4541), and the introduction of *o*- or *p*- $NO_2$  groups renders the halogen more reactive.

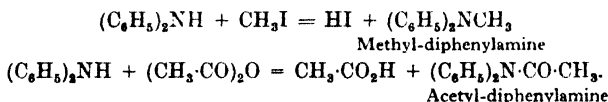
*Behaviour.*—1. The mixed secondary bases have strongly-marked basic properties, while the purely aromatic are feebler bases than the primary aliphylamines (cf. Chap. XXI, Intr.).

2. For the migration of the aliphyl group from the side chain into the nucleus see p. 430. This migration occurs when a salt of an aliphylarylamine is heated under pressure:



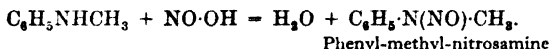
At atmospheric pressure the compound splits up into aniline and alkyl halide or olefine (J. C. S., 1931, 1281), and the reaction can be used for the preparation of certain olefines.

3. The hydrogen of the imino-group is replaceable by an alkyl or acyl radical, and also by potassium or sodium:



4. The secondary bases give neither the isonitrile nor the "mustard oil" reaction (p. 433).

5. With nitrous acid, nitrosamines are formed (cf. p. 120):



These **nitrosamines** are neutral oily liquids insoluble in water, and they regenerate the secondary bases when heated with stannous chloride or with alcohol and hydrochloric acid. With mild reducing agents they yield hydrazines.

They serve for the preparation of the pure secondary bases, since they alone are precipitated by sodium nitrite as non-basic oils from the acid solution of a mixture of primary, secondary, and tertiary bases, and yield the secondary amine with  $HCl$  and  $SnCl_2$ , or  $CuCl$  and  $HCl$  (J. C. S., 1932, 713). When such nitrosamines are digested with alcoholic hydrochloric acid, a molecular rearrangement takes place, and compounds of the nature of *p*-nitroso-methyl-aniline (p. 440),  $NO\cdot C_6H_4\cdot NHCH_3$ , are formed by molecular rearrangement (O. Fischer and Hepp, B., 19, 2991; 20, 1247). All nitrosamines give *Liebermann's* reaction (p. 474).

Analogous **nitramines**, e.g.  $\text{CH}_5\cdot\text{NMe}\cdot\text{NO}_2$ , are formed by the action of nitric acid on an alipharylamine and with mineral acids yield *o*- and *p*-nitro-compounds by the wandering of the  $\text{NO}_2$  group into the ring.

**Methyl aniline**,  $\text{C}_6\text{H}_5\cdot\text{NHMe}$ , is a colourless oil lighter than water. It is a stronger base than aniline; its **sulphate** does not crystallize, and is soluble in ether. For oxidation cf. B., 1902, 703.

**Diphenylamine**,  $\text{NHPh}_2$ , crystallizes in colourless plates, melts at  $54^\circ$ , distils at  $302^\circ$ , and its solution in sulphuric acid yields an intense blue colour with a trace of nitric acid (delicate test). The **nitrosamine**,  $\text{NPh}_2\cdot\text{NO}$ , forms yellow plates melting at  $66\cdot5^\circ$ , and the **acetyl-derivative**,  $\text{NPh}_2\cdot\text{CO}\cdot\text{CH}_3$ , melts at  $103^\circ$ . Numerous **nitro-derivatives** are known, e.g.  $[\text{C}_6\text{H}_2(\text{NO}_2)_3]_2\text{NH}$ , which is feebly acidic in properties; its ammonium salt is the dye aurantia.

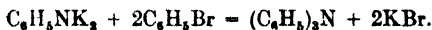
## C. Tertiary Monamines

These are either purely aromatic (triarylamines) or mixed (aliphyl-arylamines).

*Modes of Formation*.—1. The latter are formed when the primary or secondary bases are alkylated (cf. p. 437). Methyl bromide, iodide or sulphate are often used on the small scale, but on the manufacturing scale methyl alcohol and hydrochloric acid under pressure. Primary and secondary amines can be removed by the action of ethyl chloroformate, which converts them into urethanes (p. 317), and the tertiary base then dissolved by means of dilute hydrochloric acid.

A convenient laboratory method is that due to *Noelting* (B., 1891, 563; J. C. S., 1904, 236). The primary amine is heated on the water-bath with a slight excess of the alkyl iodide and sodium carbonate solution, and in many cases an almost theoretical yield of the tertiary amine is formed. Tertiary bases are also formed when the quaternary salts are strongly heated.

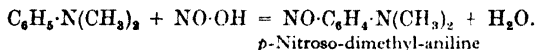
2. Triphenylamine, a purely aromatic base, is formed by the action of bromobenzene upon dipotassium-aniline:



*Behaviour.*—1. Unlike the aliphyl-arylamines, the purely aromatic tertiary amines are incapable of forming salts.

2. They do not yield isonitriles with  $\text{CHCl}_3$ , isothiocyanates with  $\text{CS}_2$ , or acyl derivatives with acid chlorides, but most of them yield quaternary compounds with methyl iodide.

3. Nitrous acid reacts with the tertiary aromatic bases, yielding coloured **nitroso-compounds** which contain the NO group linked to the benzene nucleus; but in certain cases, e.g. dimethyl-*p*-toluidine, it can act as a nitrating agent (J. C. S., 1930, 277):



Such nitroso-derivatives can be reduced to diamines and hydrolysed to nitroso-phenols.

4. The tertiary amines, when oxidized with hydrogen peroxide, yield unstable oxides, e.g. **dimethyl-phenylamine oxide**,  $\text{C}_6\text{H}_5\cdot\text{NMe}_2\cdot\text{O}$ , feebly basic compounds soluble in water, and decomposed at high temperatures (cf. Chap. I, C2).

5. Tertiary amines in which the three substituents are different, e.g. methyl-ethyl-aniline or benzyl-phenyl-hydrazine, do not exist in isomeric forms, and cannot be resolved into optically active components (*Kipping and Salway*, J. C. S., 1904, 438; *H. O. Jones and Millington*, C. C., 1904, 2, 952). The centres of gravity of the nitrogen atom and of the three substituents would therefore appear to lie in one plane.

6. Tertiary amines containing a benzyl group are decomposed by acetic anhydride, yielding benzyl acetate and the acetyl derivative of a secondary amine.

**Dimethyl-aniline**,  $\text{C}_6\text{H}_5\cdot\text{N}(\text{CH}_3)_2$ , is an oil of sharp basic odour, solidifying in the cold; its salts do not crystallize well. It combines with methyl iodide, even in the cold, to the compound  $\text{N}(\text{C}_6\text{H}_5)(\text{CH}_3)_3\text{I}$ , phenyl-trimethyl-ammonium iodide, which breaks up into its components when distilled. With nitrous acid it yields *p*-nitroso-dimethyl-aniline, which crystallizes in green plates, melting at  $85^\circ$ ; the hydrochloride crystallizes in yellow needles. When oxidized with permanganate the nitroso-compound yields *p*-nitro-dimethyl-aniline (m.-pt.  $162^\circ$ ), when reduced *p*-amino-dimethyl-aniline, and when hydrolysed with alkali *p*-nitroso-phenol (Chap. XXIV, A1) and dimethylamine. (For condensations cf. Malachite-green, Chap. XXX.) Bleaching-powder colours dimethyl-aniline only

a pale-yellow. Dimethyl-aniline yields compounds of somewhat complex composition with acid chlorides, aldehyde, &c.; for example, tetramethyl-diamino-benzophenone or, finally, methyl violet with carbonyl chloride; leuco-malachite green with benzoic aldehyde, &c. Mild oxidizing agents, such as chloranil, convert it into methyl violet. **Diethyl-aniline** boils at  $216^{\circ}$ ; its ***p*-nitroso-derivative** melts at  $84^{\circ}$ .

**Triphenyl-amine**,  $\text{NPh}_3$ , melts at  $127^{\circ}$ , and yields no salts.

### D. The Quaternary Bases

correspond with the quaternary bases of the fatty series. **Trimethyl-phenyl-ammonium hydroxide**,  $\text{C}_6\text{H}_5\cdot\text{N}(\text{CH}_3)_3\cdot\text{OH}$ , for instance, is a colourless, strongly alkaline, bitter substance which breaks up into dimethyl-aniline and methyl alcohol when heated. The salts are formed by the union of a tertiary dialkyl-arylamine with an alkyl halide or even as alkyl sulphate or the methyl ester of an aromatic sulphonic acid, e.g. methyl *p*-toluenesulphonate,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_3\text{Me}$ . This last reagent is recommended as a reagent for identifying particular tertiary amines (J. A. C. S., 1929, 3638). Most of the tertiary amines, however, which contain substituents in the two ortho-positions with respect to the alkylated  $\text{NH}_2$  group, are incapable of yielding quaternary ammonium salts, e.g. 2:6-dibromodimethylaniline,  $\text{C}_6\text{H}_3\text{Br}_2\cdot\text{NMe}_2$  (*E. Fischer*, B., 1900, 345, 1967).

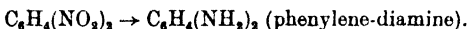
The readiness with which a given quaternary salt is formed depends to a large extent on (a) the order in which the radicals are introduced, (b) the nature of the alkyl halide used, e.g. chloride bromide or iodide, the last reacting most readily, (c) the solvent (p. 116), and (d) temperature. (Cf. *Wedekind*, A., 1901, 318, 90; *Jones*, B. A. Rep., 1904, 179. For Velocity of Formation cf. *E. R. Thomas*, J. C. S., 1913, 594.) It has been found that in the preparation of phenyl-dimethylethyl ammonium iodide a 100 per cent yield is obtained when methylethyl-aniline is combined with methyl iodide, but only a 15 per cent when dimethyl-aniline is combined with ethyl iodide under similar conditions. Two factors affect the velocity of formation: (1) The anionization of the halogen of the alkyl halide. (2) The co-ordination of the N atom of the base, by means of its lone pair of electrons, with the  $\text{CH}_3$ , and this

is facilitated by an electron recession from the halogen. Substituents in the aliphyl halide determine the probability of 1 or 2 (*Baker*, J. C. S., 1932, 1148; *Davies*, *Evans* and *Hulbert*, 1939, 412).

All the quaternary compounds so far discussed contain 4 alkyl and 1 negative radical (e.g. OH, Cl), attached to nitrogen; compounds of the type  $\text{NR}_5$  are known (*Schlenk*, B., 1917, 274, 823), e.g.  $\text{NMe}_4 \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$ , a red powder obtained from  $\text{NMe}_4\text{Cl}$  and  $\text{C}_6\text{H}_5 \cdot \text{CH}_2\text{Na}$  (cf. *Chap. L*, C2).

### E. Diamines, Triamines, &c.

Polyamino-derivatives may be obtained by reducing poly-nitro-hydrocarbons or nitro-amino-compounds, e.g.:



The *o*- and *p*-diamines are best obtained from the *o*- and *p*-nitro-amino-compounds. Tetramino-benzene is formed in an analogous manner by reducing dinitro-*m*-diamino-benzene.


A new amino-group can be introduced in the *p*-position into an arylamine, especially a secondary or tertiary, such as  $\text{C}_6\text{H}_5 \cdot \text{N}(\text{CH}_3)_2$ , by first transforming the latter into an azo-dye (e.g. benzene-azo-dimethyl-aniline,  $\text{C}_6\text{H}_5 \cdot \text{N} : \text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{NMe}$ ) by coupling it with benzene-diazonium chloride, and decomposing this by reduction. (See the Azo-compounds.)

Diamines are also formed by the reduction of the nitroso-compounds of tertiary amines; *p*-amino-dimethyl-aniline,  $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{N}(\text{CH}_3)_2$ , from *p*-nitroso-dimethyl-aniline.

The polyamines are solid compounds which crystallize in plates and distil unchanged, and are soluble in warm water. Though originally without colour, most of them quickly become brown in the air, their instability increasing with the number of amino-groups present. In accordance with the readiness with which they are oxidized, they frequently yield characteristic colorations with ferric chloride, e.g. *o*-phenylene-diamine a dark-red, and 1 : 2 : 3-triamino-benzene a violet and then a brown colour.

The three isomeric groups of diamines differ materially in their behaviour.

(a) **Ortho-diamines**.—1. Ferric chloride yields a yellowish-red crystalline precipitate of diamino-phenazine hydrochloride,

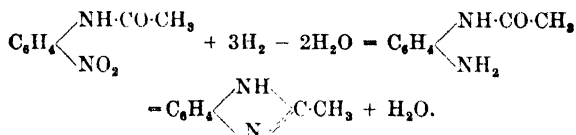
$\text{C}_6\text{H}_4$    $(\text{C}_6\text{H}_2(\text{NH}_2)_2)_2, 2\text{HCl}$ , with a solution of *o*-phenylene-diamine.

2. Ortho-diamines yield azomethines with aromatic aldehydes, e.g.  $\text{C}_6\text{H}_4(\text{N}:\text{CHR})_2$ , but these readily change into cyclic compounds, e.g.:



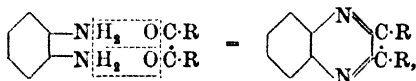
when  $\text{R} = \text{C}_6\text{H}_5$ .

3. The mono-acyl compounds of the *o*-diamines change into derivatives of iminazole (A., 273, 269), the so-called "*Benziminazoles*" or "*Anhydro-bases*", through the formation of intramolecular anhydrides; thus *o*-nitracetanilide, when reduced with tin and hydrochloric acid, yields methyl-benziminazole or phenylene-ethenyl-amidine (A., 209, 339):



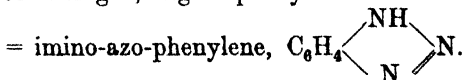
Compounds of this nature are also obtained by heating *o*-diamines with acids.

4. Glyoxal and many of the  $\alpha$ -diketones yield quinoxaline and its derivatives with *o*-diamines:



and the  $\alpha$ -ketonic alcohols react in an analogous manner, e.g. benzoin yields dihydro-diphenyl-quinoxaline.

5. Nitrous acid converts the *o*-diamines into the so-called "azimino-compounds", compounds which contain three atoms of nitrogen, e.g. *o*-phenylene-diamine into azimino-benzene



(b) **Meta-diamino-bases.**—1. These form yellow-brown dyes with nitrous acid, even when only traces of the latter are present (see Bismarck Brown, Chap. XXII. E.).

2. They yield azo-dyes with benzenediazonium chloride (see Chrysoidine, Chap. XXII, E.).

3. With nitroso-dimethyl-aniline, or on oxidation together with para-diamines, blue colouring-matters (indamines) are obtained, and these when boiled yield red dyes (see Toluylene red).

(c) **Para-diamino-compounds**.—1. When warmed with ferric chloride, or better, with  $\text{MnO}_2 + \text{H}_2\text{SO}_4$ , quinone,  $\text{C}_6\text{H}_4\text{O}_2$  (or a homologue), is formed, and may be recognized by its odour.

2. By oxidizing para-diamines, containing one amino-group, together with a monamine or a meta-diamine, indamines are produced, giving blue-green coloration.

## F. Acyl Derivatives of Arylamines. Anilides, &c.

Acyl derivatives of primary and secondary arylamines are formed (a) by heating with the acid, (b) by the action of the acyl chloride or anhydride in the presence of a little conc. sulphuric acid. The commonest are the **acetyl** derivatives, e.g.  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ ,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ ,  $(\text{C}_6\text{H}_5)_2\text{N}\cdot\text{CO}\cdot\text{CH}_3$ , &c. The acyl products formed from aniline are termed anilides (p. 432), e.g. acetanilide, benzanilide, oxanilide; they are really phenylated acid amides (see p. 209 *et seq.*), and as such may be hydrolysed, although not so readily as the amides, by means of acids or alkalis, to aniline and the corresponding acid. Tertiary amines form additive compounds with acyl chlorides which are decomposed by water.

The dibasic acids like oxalic acid can give rise not merely to anilides, e.g.  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{CO}\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_5$ , oxanilide, but also to half anilides, the **anilic acids**, which correspond with the amic acids, e.g. oxanilic acid,  $\text{C}_6\text{H}_5\text{NH}\cdot\text{CO}\cdot\text{CO}\cdot\text{OH}$ . These are monobasic acids, and can also be hydrolysed to their components.

Similarly, the toluidines give rise to **toluidides**, e.g. acetoluidide,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ , and the xylidines likewise give rise to **xylidides**, &c.

The acetyl derivatives are frequently used for the identification of the various primary and secondary arylamines, since they crystallize well and have definite melting-points. As a rule, it is sufficient to mix the amine with a slight excess of acetic anhydride and warm for two minutes, and then to

pour into water. After a short time the solid (or oily) acetyl derivative is obtained.

**Formanilide**,  $C_6H_5 \cdot NH \cdot CH : O$ , from aniline and formic acid, reacts as a tautomeric substance, and gives rise to two series of alkyl derivatives, one with alkyl attached to N, and the other with alkyl attached to O, the imino-ethers.

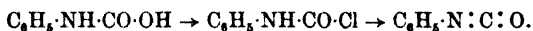
**Acetanilide**,  $C_6H_5 \cdot NH \cdot CO \cdot CH_3$ , is most conveniently prepared by boiling aniline with glacial acetic acid for twenty-four hours. It crystallizes in beautiful white prisms which are readily soluble in hot water or alcohol, less readily in ether and benzene. It melts at  $115^\circ$ , and boils at  $304^\circ$ . In the absence of water it can form a hydrochloride,  $C_7H_9ON$ , HCl. Acetanilide ("antifebrine") is used in medicine for reducing high temperatures.

With  $PCl_5$  it gives  $C_6H_5 \cdot NH \cdot CCl_2 \cdot CH_3$ , which loses HCl, giving an *imino chloride*  $C_6H_5N : CCl \cdot CH_3$ .

**Thio-acetanilide**,  $C_6H_5 \cdot NH \cdot CS \cdot CH_3$ , is formed when acetanilide is heated with phosphorus pentasulphide, and from it **imido-thio-compounds**, **amidines**, &c., can be prepared. **Methyl-acetanilide**,  $C_6H_5 \cdot N(CH_3)(C_2H_5O)$ , is used as a specific against headache.

**Oxanilide**,  $C_6H_5 \cdot NH \cdot CO \cdot CO \cdot NH \cdot C_6H_5$ , is obtained when aniline oxalate is heated at  $160^\circ$ – $180^\circ$ . It melts at  $252^\circ$ , boils without decomposition, and is best hydrolysed by fusion with potash.

The half anilide, **oxanilic acid**,  $COOH \cdot CO \cdot NH \cdot C_6H_5$ , is formed when aniline oxalate is heated at  $130^\circ$ – $140^\circ$ . It melts at  $149^\circ$ – $150^\circ$ , is soluble in hot water, has the properties of a monobasic acid, and with phosphorus pentachloride yields phenyl-carbimide (phenyl isocyanate):



Diacyl derivatives of aniline and its homologues are also known, e.g.  $C_6H_5 \cdot N(CO \cdot CH_3)_2$ , **diacetanilide**. This is formed, together with acetanilide, when aniline is boiled for an hour with excess of acetic anhydride, or when the amine is heated to a high temperature with acetyl chloride. The two may be separated by fractional distillation under diminished pressure. The diacetanilide crystallizes in colourless prisms, melts at  $37^\circ$ , and, unlike acetanilide, is readily soluble in benzene or light petroleum. On hydrolysis with dilute alkali, one acetyl group is split off more readily than the second.

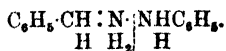


The presence of one or two substituents in the *o*-position with respect to the amino-group of aniline facilitates the formation of diacetyl derivatives, e.g. *o*-toluidine yields a diacetyl derivative more readily than aniline, and *s*-tribrom-aniline yields a diacetyl derivative with the greatest readiness (J. C. S., 1901, 533).

In nearly all those compounds of the fatty series which are amino- or imino-derivatives of alcohols, acids, or hydroxy-acids, the unreplaced amino hydrogen can be substituted indirectly either wholly or partially by phenyl. The number of these phenylated (tolylated, xylylated, &c.) compounds is thus extremely large. Among them may be mentioned: **Phenyl-glycocoll**, *Phenyl-glycine*,  $C_6H_5 \cdot NH \cdot CH_2 \cdot CO_2H$ , from chloracetic acid and aniline; **phenyl-imino-butyric acid**,  $CH_3 \cdot C(:NC_6H_5) \cdot CH_2 \cdot CO_2H$ , from aniline and aceto-acetic ester; **carbanilide** or diphenyl-urea,  $CO(NHC_6H_5)_2$ , from aniline and carbon oxychloride (cf. p. 316); **phenyl isocyanate**, *phenyl carbimide*,  $CO:N \cdot C_6H_5$ , from  $COCl_2$  and fused aniline hydrochloride, a sharp-smelling liquid exactly analogous to the isocyanic esters—its vapour gives rise to tears; **phenyl isothiocyanate**,  $C_6H_5N:CS$  (b.-pt.  $222^\circ$ ), a liquid possessing all the characteristics of the mustard oils (p. 312); **diphenyl thio-urea**,  $CS(NHC_6H_5)_2$ , from aniline and carbon disulphide (forms glistening plates, melting at  $154^\circ$ ; it is decomposed into phenyl isothiocyanate and aniline when hydrolysed with concentrated hydrochloric acid.

### G. Primary Amines with the Amino-group in the Side Chain

These compounds resemble the primary aliphylamines much more closely than aniline. **Benzylamine**,  $C_6H_5 \cdot CH_2 \cdot NH_2$ , the amine corresponding with benzyl alcohol, is a colourless liquid which distils unchanged. The acetyl compound,  $C_6H_5 \cdot CH_2 \cdot NH \cdot CO \cdot CH_3$ , is formed by heating benzyl chloride,  $C_6H_5 \cdot CH_2Cl$ , with acetamide. Benzylamine is formed, together with di- and tri-benzylamines, by the action of alcoholic ammonia on benzyl chloride; it is also readily obtained by reducing the phenyl-hydrazone of benzaldehyde:



It may also be prepared from benzyl chloride and potassium phthalimide (cf. Chap. XXVI, B.). Its behaviour is entirely analogous to that of methylamine, as the phenyl derivative of which it is to be regarded. It dissolves in water, and the solution thus formed is alkaline. Conductivity determinations show that it is about as strong a base as ammonia, and thus differs materially from aniline. It possesses all the characteristic properties of a primary amine, but as the  $\text{NH}_2$  is attached to a side chain and not to the benzene nucleus, on treatment with nitrous acid it immediately yields benzyl alcohol and not a diazonium salt.

## XXII. DIAZO- AND AZO-COMPOUNDS; HYDRAZINES

### A. Diazo-compounds \*

The primary arylamines differ characteristically from the primary aliphylamines in their behaviour towards nitrous acid. Most of the latter are converted into alcohols without the formation of intermediate products (cf. p. 119):



The aromatic amines can undergo an analogous transformation; but if the temperature is kept sufficiently low, well-characterized intermediate products, the **diazonium salts**, e.g. benzene-diazonium chloride,  $\text{C}_6\text{H}_5\text{N}_2\text{Cl}$ , are obtained, which are of especial interest both scientifically and technically (cf. Azo-dyes, Chap. XXII, E.). They were discovered by *P. Griess* in 1860, and were carefully investigated by him (A., 121, 257; 137, 39).

The diazo-compounds are usually divided into (1) the diazonium salts, e.g.  $\begin{array}{c} \text{C}_6\text{H}_5 \\ \text{Cl} \end{array} \text{N} \equiv \text{N}$ , compounds which are analogous

\* Aromatic Diazo-compounds (*Sanders*, London, 1936, C. and I., 1936, 192).

to ammonium salts; (2) the true diazo-compounds, which contain the grouping  $\cdot\text{N}:\text{N}\cdot$ .

**I. Diazonium Compounds.**—The diazonium salts, as a rule, are not obtained in the solid state, as they themselves are of little commercial value, but are of importance as intermediate products in various decompositions.

Solutions are usually prepared by the addition of an aqueous solution of sodium nitrite to a solution of the amine in an excess of the requisite acid (*V. Meyer*). The essentials are: (1) The solution must be kept cool, at  $0^\circ$  or only a few degrees above, otherwise a phenol is formed and nitrogen evolved. (2) An excess of acid must be used, otherwise diazo-amino-compounds (Chap. XXII, B.) are formed. (3) As a rule, it is advisable not to use an excess of nitrous acid. This is avoided by testing for free nitrous acid by means of potassium iodide starch paper.

Amino-compounds which do not dissolve readily in dilute acid, e.g. *s*-tribromaniline, can be diazotized by using conc. sulphuric, or sometimes hydrobromic acid, and adding nitrosyl-sulphuric acid  $\text{NOHSO}_4$ .

This conversion of amino- into diazo-compounds is termed “**diazotizing**”.

The crystalline salts, e.g. benzene-diazonium chloride, may be obtained by adding concentrated hydrochloric acid to an alcoholic solution of aniline hydrochloride, and then amyl or ethyl nitrite (*Knoevenagel*). They may also be obtained by the addition of alcohol and ether to their aqueous solutions. Sparingly soluble salts can be prepared by adding solutions of sodium chromate, picrate, ferrocyanide to aqueous solution of the diazonium sulphate, but are extremely sensitive to light or shock and explode with great violence.

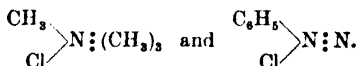
**Constitution.**—The  $\text{N}_2\text{X}$  group can be attached to only one carbon atom of the benzene nucleus, since (1) when the salts undergo decomposition the products formed contain groups, e.g.  $\text{Cl}$ ,  $\text{OH}$ ,  $\text{CN}$ , &c., which are attached to a single carbon atom; (2) penta-substituted anilines, e.g.  $\text{SO}_3\text{H}\cdot\text{C}_6\text{Br}_4\cdot\text{NH}_2$ , can be diazotized, hence *Griess*' formulae, e.g.  $\text{C}_6\text{H}_4\text{N}_2$ ,  $\text{HCl}$ , where the diazo-radical replaces two hydrogen atoms of the nucleus, are untenable.

For many years *Kekulé*'s structural formula,  $\text{C}_6\text{H}_5\cdot\text{N}:\text{N}\cdot\text{Cl}$ , analogous to that of true azo-compounds, was accepted, but has been replaced by one suggested by *Blomstrand* in 1875.

This represents the molecule of a diazonium salt as containing a quinquevalent nitrogen atom, e.g.  $\begin{array}{c} \text{C}_6\text{H}_5 \\ \text{Cl} \end{array} \text{N}^+ \text{:N}$ . The chief

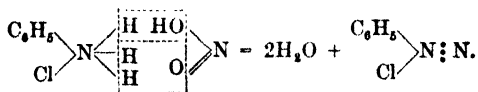
arguments in favour of the *Blomstrand* formula are briefly:

1. It indicates the resemblance between the diazonium and ammonium or quaternary ammonium salts, as both thus contain quinquevalent nitrogen:



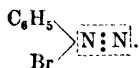
The resemblance between the two groups of compounds is marked. The diazonium salts are colourless crystalline compounds readily soluble in water; those derived from strong acids, e.g. the chlorides, nitrates, and sulphates, are neutral in solution, cf.  $\text{NH}_4\text{Cl}$ ; whereas those derived from feeble acids, e.g. carbonic acid, are partially hydrolysed in aqueous solution, and hence give an alkaline reaction, cf.  $\text{Na}_2\text{CO}_3$  or  $(\text{NH}_4)_2\text{CO}_3$ . In addition they form sparingly soluble platinichlorides,  $(\text{C}_6\text{H}_5\text{N}_2)_2\text{PtCl}_6$ , and aurichlorides,  $\text{C}_6\text{H}_5\text{N}_2\text{AuCl}_4$ , comparable with the ammonium compounds, and also polyhalide salts, e.g.  $\text{C}_6\text{H}_5\text{N}_2\text{ICl}_2$  and  $\text{C}_6\text{H}_5\text{N}_2\text{IBr}_2$ . The aqueous solutions of the salts are ionized to much the same extent as the corresponding quaternary ammonium salts. This resemblance of the diazonium ions to the quaternary ammonium ions is further established by a comparison of migration values. The free base, benzene-diazonium hydroxide, corresponding with ammonium hydroxide, is obtained by the action of moist silver oxide on the chloride; it dissolves readily in water, yielding strongly alkaline solutions, but is very unstable, and gradually decomposes. When neutralized with acids, it yields the above-mentioned diazonium salts.

2. The conversion of aniline and its homologues into diazonium salts is rendered somewhat more simple by such a formula:



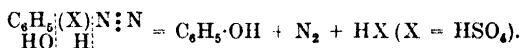
3. The elimination of nitrogen and the formation of mono-

substituted-compounds, e.g.  $\text{C}_6\text{H}_5\cdot\text{OH}$ ,  $\text{C}_6\text{H}_5\text{Br}$ , &c., is readily explicable:

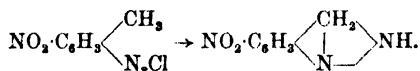


*Reactions.*—1. The reaction characteristic of the diazonium salts is the readiness with which nitrogen is eliminated and monovalent groups are introduced into the molecule in place of the  $\text{N}_2\text{X}$  radical, and for this reason the diazonium compounds are frequently made use of in the laboratory for the preparation of various substituted benzene derivatives. Examples of this type of reaction are:

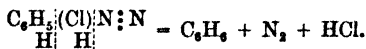
(a) *Replacement of  $\text{N}_2\text{X}$  by OH.*—An aqueous solution of a diazonium salt, especially the sulphate, evolves all its nitrogen in the form of gas when warmed, and a phenol is formed:



This reaction, which is of almost universal application, therefore allows the exchange of  $\text{NH}_2$  for OH. Exceptions are salts containing numerous negative substituents in the benzene nucleus, e.g.  $\text{C}_6\text{H}_2\text{Br}_3 \cdot \text{N}_2\text{Cl}$ , and bases with a methyl group ortho to the amino-group, when diazotization followed by warming with acid produces ring formation and an indazole is obtained:



(b) *Replacement by H.*—When diazonium salts, either in the solid state or dissolved in concentrated sulphuric acid, are heated to boiling with absolute alcohol, the diazo-group is generally replaced by hydrogen. In this reaction the alcohol gives up two hydrogen atoms, and is oxidized to aldehyde:



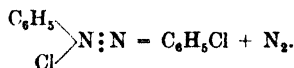
This affords a simple method for the replacement of  $\text{NH}_2$  by H.

With certain salts there is an exchange of the diazo-group for the alkoxy-radical, with the formation of ethers of phenols; thus from chlorinated toluidines ethyl ethers of chloro-cresols are formed, and not chloro-toluenes, and whether H or OR replaces the diazonium group depends on the

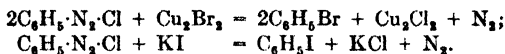
alcohol used and on the substituents present in the benzene ring (B., 1901, 3337; 1903, 2061).

Under certain conditions stannous chloride in alkaline solution acts in an analogous manner (B., 1889, 587), while under others it gives rise to hydrazines (this Chap., D.). The  $\text{NH}_2$  may also be replaced by H, by first converting into a hydrazine, and then decomposing the latter with *Fehling's* solution (Baeyer, B., 1885, 89).

(c) *Replacement by Halogen—Sandmeyer's Reaction.*—When a diazonium-compound is warmed with a concentrated solution of cuprous chloride in hydrochloric acid, the diazo-group is replaced by chlorine (Sandmeyer, B., 1884, 1633, 2650; 1890, 1628; A., 272, 143). The same reaction takes place on distilling the diazonium platinichloride with soda, and sometimes on simply treating the diazo-compound itself with fuming hydrochloric acid, or with hydrochloric acid in presence of copper powder (Gattermann, B., 1890, 1218):

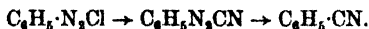


Warming with cuprous bromide yields, in the same way, a bromo-derivative (Sandmeyer, B., 1885, 1482), and treatment with hydriodic acid or potassium iodide an iodo-compound:



When  $\text{NO}_2$  groups are present a secondary reaction may occur resulting in the formation of diphenyl derivatives (Chap. XXVII), and which of the two reactions predominates depends on the conditions of the experiment. *Ullmann* and others, B., 1901, 3802; 1905, 725.

(d) *Replacement by .CN.*—This is accomplished by adding the diazotized solution to a warm solution of potassium cuprous cyanide:



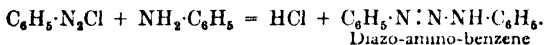
This reaction is of importance, as the product obtained is a nitrile, and can be hydrolysed to an acid.

(e) Phenyl sulphide is formed by the action of hydrogen sulphide on benzene-diazonium chloride (cf. B., 1882, 1683); nitro-benzene is formed by the action of nitrous acid in

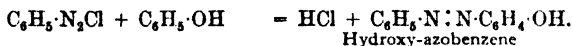
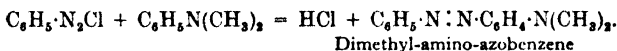
presence of cuprous oxide; benzenesulphinic acid from sulphurous acid (*J. Thomas*, *J. C. S.*, 1909, 342); phenyl thiocyanate from thiocyanic acid; and phenyl cyanate from cyanic acid, &c. (cf. *B.*, 1890, 738, 1218, 1454, 1628; 1892, 1086; 1893, 1996).

(f) When oxidized in alkaline solution, benzene-diazonium hydroxide yields—together with other products—nitroso-benzene (p. 426), and much **benzene-diazoic acid**,  $C_6H_5 \cdot N \cdot NO \cdot OH$ , or its isomeride, **phenyl-nitramine**,  $C_6H_5 \cdot NH \cdot NO_2$  (m.-pt.  $46^\circ$ ; explodes at  $98^\circ$ ) (see *B.*, 1893, 471; 1894, 584, 915).

2. When a solution of a diazonium compound reacts with a primary or secondary amine, or when nitrous acid acts upon such an amine in the absence of free mineral acid, diazo-amino-compounds are formed, and these readily change into amino-azo-compounds:



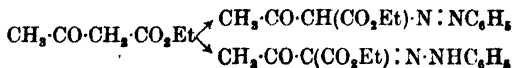
3. **Azo-dyes.**—The diazonium salts readily “couple” with tertiary amines or with phenols, yielding derivatives of azobenzene, e.g.:



Such derivatives possess basic or acidic properties, are usually coloured yellow, red, or brown, and are known as azo-dyes.

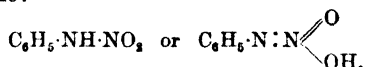
The formation of such an azo-dye is largely made use of as a test for a primary aromatic amine with the  $NH_2$  in the nucleus. The amine is dissolved in acid, diazotized, and then mixed with an alkaline solution of a phenol (preferably  $\beta$ -naphthol), when an orange-red dye is precipitated. Phenolic ethers also couple with diazonium salts (*Meyer and Wertheimer*, *A.*, 1913, 398, 66; *B.*, 1914, 1741; *Auwers and Michaelis*, *ibid.* 1275).

4. The diazonium salts react in alkaline solution with compounds containing the grouping  $\cdot CH_2 \cdot CO \cdot$ , yielding azo-compounds or phenylhydrazones, e.g.:



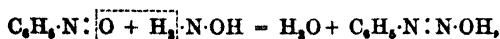
(cf. *B.*, 1888, 1697).

**II. Diazo-compounds.**—These contain the grouping  $R:N:N\cdot X$ , where  $R$  = an aryl radical and  $X$  an acid radical or  $OH$  or  $OK$ . When a benzene-diazonium salt is mixed with an excess of cold concentrated alkali, normal potassium benzene-diazotate,  $C_6H_5N_2OK$ , is precipitated. It crystallizes in white plates, and can be quantitatively converted into benzene-diazonium chloride and couples with  $\beta$ -naphthol; it yields ethers, and on oxidation gives nitroso-benzene and phenylnitramine:



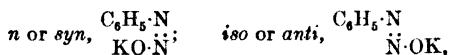
The acid,  $C_6H_5N_2OH$ , which corresponds with the potassium salt, is not known in a pure form. When the **normal** potassium salt is heated with concentrated potash at  $130^\circ$ – $135^\circ$ , it is transformed into an isomeric potassium salt (*Schraube* and *Schmidt*, B., 1894, 520). When this is acidified with acetic acid, the free **hydroxide** is obtained as a colourless oil which is very unstable. It is acidic and quite unlike the unstable benzene-diazonium hydroxides.

Similar *normal* and *isopotassium* derivatives have been obtained from other diazonium salts, and it has been found that the presence of acylous groups ( $Br$ ,  $NO_2$ ) facilitates the formation of the iso-compound—in fact to such an extent that certain diazonium salts, when added to an alkali, immediately yield the isodiazo-compounds. The researches of *Hantzsch* have proved that the two compounds are very similar as regards chemical properties. For example, both “couple” with alkaline solutions of phenols, yielding azo-dyes (this Chap., E.), but the normal much more readily than the iso-compounds. Both compounds, on reduction with sodium amalgam in the presence of a large excess of alkali, yield phenyl-hydrazine, and both compounds, on oxidation in alkaline solution, yield the potassium salt,  $C_6H_5\cdot N:NO\cdot OK$ , or the tautomeric nitramine. Similarly, both compounds yield the same benzoyl derivative by the *Schotten-Baumann* method. Hence the two compounds are structurally identical and *stereo-isomeric*. As the normal can be synthesized by the action of hydroxylamine on nitroso-benzene in alkaline solution (*Hantzsch*, B., 1905, 2056):





it is probable that both normal and iso-compound are true diazo-derivatives, and that they are stereo-isomeric in much the same manner as the oximes (p. 163). According to *Hantzsch*, the normal compound has the *syn*- and the iso- the *anti*-configuration:

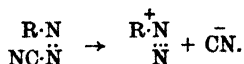


as the normal compounds evolve nitrogen very readily, whereas the iso-compounds are more stable. (Ber., 1894, 1702; 1895, 676, 1734; 1903, 4054; 1904, 1084).

The iso-diazotates can react as tautomeric compounds, viz. as nitrosamine derivatives,  $C_6H_5 \cdot NK \cdot NO$ , since the potassium salt yields an N-ether,  $C_6H_5 \cdot N \ddot{E}t \cdot NO$ , whereas the silver salt yields an O-ether,  $C_6H_5 \cdot N : N \cdot OEt$ . Certain diazo-hydroxides,  $R \cdot N_2 \cdot OH$ , have been isolated as colourless solids with acidic properties; the majority, however, are extremely unstable, and pass over into the isomeric nitrosamines  $R \cdot NH \cdot NO$ , yellow compounds with neutral properties (B., 1902, 2964; 1903, 4054; 1904, 1084). The effect of various solvents on this isomerization has been studied by *Bamberger* and *Baudisch* (B., 1912, 2054). *p*-Nitrophenyl-nitrosamine in ether or alcohol has the diazo structure, but in chloroform the nitrosamine formula. On oxidation they yield nitramines.

Corresponding with the normal and iso-diazotates, *Hantzsch* has isolated two groups of sulphonates and of cyanides, which he also regards as being stereo-isomeric in the same sense, viz. *syn* and *anti*.

In the case of *p*-anisidine, evidence of the existence of three isomeric diazo-cyanides has been obtained. The one is colourless and is an electrolyte, and hence is regarded as the diazonium salt,  $OMe \cdot C_6H_4 \cdot N(CN) : N$ ; the other two are reddish-coloured solids and non-electrolytes. The *syn*-compound is unstable, and melts at  $51^\circ$ ; it gradually passes over into the more stable *anti*-compound, which melts at  $121^\circ$ . It is probable that when a *syn* diazo-cyanide is dissolved in water it is largely transformed into the ionized diazonium cyanide:

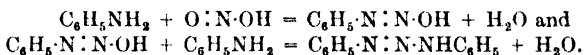


Diazonium salts, *n*-diazotates and the labile diazo-sulphonates react with sodium arsenite or a mixture of KCN and

NaHS in such a manner that the  $N_2X$  group is replaced by hydrogen, whereas iso-diazotates, stable diazo-sulphonates, azo- and azoxy-compounds do not react (*Gutmann, B., 1912, 821*).

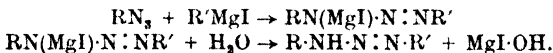
## B. Diazo-amino-compounds

The diazo-amino-compounds are pale-yellow crystalline substances which are stable in the air, and do not combine with acids. They are obtained by the action of a primary or secondary amine on a diazonium salt, and also when nitrous acid reacts with a free primary aromatic amine instead of with its hydrochloride, probably:



As they are extremely sensitive to acids it is essential to avoid excess of acid in their preparation, and acetic acid or carbonic anhydride is recommended for liberating the nitrous acid from its sodium salt.

Diazo-amine compounds have been synthesized by the action of *Grignard* compounds on alkyl or acyl derivatives of hydrazoic acid, and decomposing the products with water:

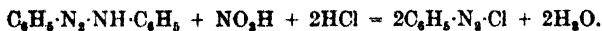


In this manner not merely aromatic but aliphyl-aryl compounds of the types  $C_6H_5.NH:N:N.CH_3$  and  $C_6H_5.CH_2.NH:N:N.CH_3$  have been prepared.

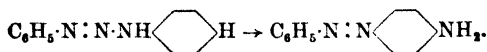
*Reactions.*—1. They are not bases, and hence do not form salts with acids, but have feebly acidic properties yielding metallic salts, e.g.  $RNK:N:NR$  with alcoholic potash.

2. They behave in much the same way as the diazonium compounds, as they are usually decomposed in the first instance into their components, a diazonium salt and an amine. Thus diazo-amino-benzene yields phenol and aniline when boiled with water or hydrochloric acid, while with hydrobromic acid it gives bromobenzene and aniline. These reactions are easy to recognize from the accompanying evolution of nitrogen.

3. Nitrous acid in acid solution completely transforms them to diazonium salts:



4. Most of them readily undergo molecular transformation into the isomeric amino-azo-compounds (*Kekulé*):



This molecular rearrangement takes place most readily in presence of an amine hydrochloride, which acts as a catalytic agent. The amino-group always takes up the para-position with regard to the azo-group ( $\cdot\text{N}:\text{N}\cdot$ ) if this is free. If, however, this is already substituted, as in the diazo-amino-compound from *p*-toluidine, then the transformation occurs much more slowly, and the  $\text{NH}_2$  takes up the *o*-position with respect to the  $\cdot\text{N}:\text{N}\cdot$  group. The velocity of transformation has been investigated by *H. Goldschmidt*, and the reaction has been shown to be unimolecular. Only a relatively small amount of aniline salt is required, and the velocity is proportional to the strength of the acid, the aniline salt of which is used (*B.*, 1896, 1899). For other transformations cf. Chap. XXXVIII.

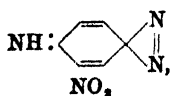
5. The imino-hydrogen of the diazo-amino-compounds is replaceable by metallic radicals, and alkyl and acyl groups.

*Constitution.*—By the action of benzene-diazonium chloride upon *p*-toluidine, "diazo-benzene-*p*-toluidide" is formed, and would appear to possess the formula:  $\text{C}_6\text{H}_5\cdot\text{N}:\text{N}\cdot\text{NH}\cdot\text{C}_7\text{H}_7$  (I).

But the same compound is also obtained from a mixture of *p*-toluene-diazonium chloride and aniline, a reaction which would indicate the constitution:  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{N}:\text{N}\cdot\text{C}_7\text{H}_7$  (II). The diazo-amino-compounds are typical tautomeric substances (cf. Chap. LIII).

**Diazo-amino-benzene**,  $\text{C}_6\text{H}_5\cdot\text{N}:\text{N}\cdot\text{NHC}_6\text{H}_5$  (*Griess*), is usually prepared by adding  $\text{NaNO}_2$  (1 mol.) to the solution of aniline (2 mols.) in  $\text{HCl}$  (3 mols.), and saturating with sodium acetate (*B.*, 1884, 641; 1886, 1952). It crystallizes in bright yellow lustrous plates or prisms, is insoluble in water, but readily soluble in hot alcohol, ether, and benzene, melts at  $98^\circ$ , and is far more stable than the diazo-compounds.

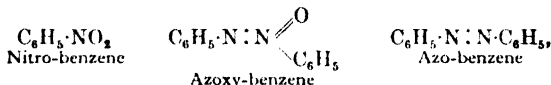
When certain *p*-diamines, e.g. *o*-nitro-*p*-phenylenediamine, are diazotized with liquid nitrous anhydride, **diazotamines**, e.g.



are formed, and these yield stable acetyl derivatives (*Morgan* and others, J. C. S., 1917, 187; 1918, 588).

### C. Azo-compounds, and Compounds intermediate between the Nitro- and Amino-compounds

While the reduction of nitro-compounds in acid solution leads to the aromatic amines, the use of alkaline reducing agents, such as sodium amalgam, zinc dust and caustic soda, and also potash and alcohol, gives rise for the most part to intermediate products, the azoxy-, azo-, and hydrazo-compounds:



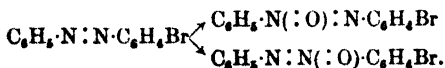
and hydrazo-benzene,  $\text{C}_6\text{H}_5\text{NH}\cdot\text{NHC}_6\text{H}_5$ . Reduction in neutral solution yields phenyl-hydroxyl-amines,  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{OH}$ .

#### 1. AZOXY-COMPOUNDS

The azoxy-compounds are mostly yellow or red crystalline substances which are obtained by the action of boiling alcoholic potash, sodium methoxide (*Brühl*, B., 1904, 2076), or magnesium amalgam and alcohol (J. A. C. S., 1904, 1161) upon the nitro-compounds. Many are also formed by the oxidation of azo-compounds. They are neutral, and are very readily reduced to azo-compounds.

**Azoxy-benzene**,  $(\text{C}_6\text{H}_5)_2\text{N}_2\text{O}$  (*Zinin*), forms pale-yellow needles melting at  $36^\circ$ , is insoluble in water, but dissolves readily in alcohol and ether. Concentrated sulphuric acid transforms it into the isomeric *p*-hydroxy-azo-benzene,  $\text{C}_6\text{H}_5\text{N}:\text{N}\cdot\text{C}_6\text{H}_4\cdot\text{OH}$ .

For a number of years the *sym.* structure  $\begin{array}{c} \text{PhN} \\ \parallel \\ \text{PhN} \end{array} \text{O}$  was accepted. *Angeli's* demonstration of the formation of two isomeric azoxy-compounds from an *unsym.* azo-compound renders such a formula untenable.

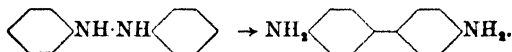


For confirmation cf. *Robinson* (J. C. S., 1917, 111), who shows that one nitro-group can be introduced quite readily into azoxy-veratrole, but that the introduction of a second can only be accomplished with difficulty.

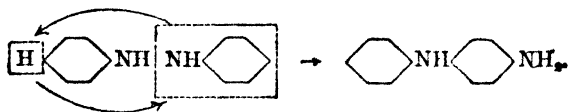
## 2. HYDRAZO-COMPOUNDS

These are colourless crystalline neutral compounds, and, like the azo-compounds, cannot be volatilized without decomposition; e.g. hydrazo-benzene decomposes into azo-benzene and aniline when heated. They are obtained by the reduction of azo-compounds with ammonium sulphide or zinc dust and alkali, or by sodium hyposulphite. Oxidizing agents, such as ferric chloride, readily transform them into azo-compounds, a reaction which also occurs when the hydrazo-compounds are exposed to the air. Stronger reducing agents, e.g. sodium amalgam, convert them into amino-compounds.

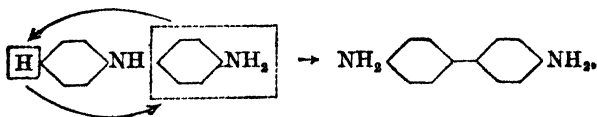
Strong acids cause them to change into the isomeric derivatives of diphenyl (Chap. XXVII and L, A5); thus from hydrazo-benzene and hydrochloric acid benzidine hydrochloride (the hydrochloride of *pp'*-diamino-diphenyl is formed):



This rearrangement is typical, and is often observed in the case of aromatic compounds. It may be regarded as the shifting or wandering of a radical—in this case the relatively complex  $\text{C}_6\text{H}_5\text{NH}\cdot$ —from attachment to the side chain to direct attachment to the benzene nucleus, or, in other words, the  $\text{NH}\cdot\text{C}_6\text{H}_5$  group exchanges place with the hydrogen atom in the *p*-position in the nucleus:

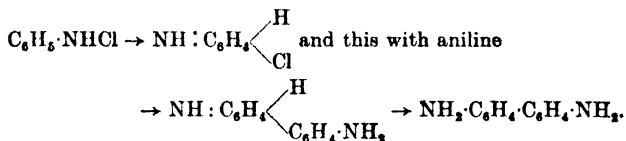


The operation is repeated,



and *pp'*-diamino-diphenyl, benzidine, is formed.

Another method of representing the change is by assuming the addition of HCl to the hydrazo-benzene and its resolution into  $C_6H_5 \cdot NH_2$  and  $C_6H_5 \cdot NHCl$ . Then



(A., 1916, 412, 14. For further details cf. Chap. XXXVIII.)

**Hydrazo-benzene**, *sym.-Diphenyl-hydrazine*,  $C_6H_5 \cdot NH \cdot NH \cdot C_6H_5$  (*Hofmann*), forms colourless plates of camphor-like odour, which are only slightly soluble in water, but dissolve readily in alcohol and ether; m.-pt.  $131^\circ$ . The imino-hydrogen atoms are replaceable by acetyl- or nitroso-groups.

When kept it undergoes spontaneous decomposition into a mixture of azo-benzene and aniline.

A group of compounds allied to the hydrazo-derivatives has been described by *Schlenk* (B., 1917, 276), e.g. **di-*p*-tolylammonium-tetramethylammonium**,  $NMe_4 \cdot N(C_7H_7)_2$ , which forms greenish-yellow crystals from pyridine. It is formed from  $NMe_4Cl$  and  $(C_7H_7)_2NK$ , is oxidized by the air, and is hydrolysed by water to ditolylamine and  $NMe_4 \cdot OH$ . Its pyridine solution is an electrolyte.

### 3. AZO-COMPOUNDS

The azo-compounds are red or yellowish-red, crystalline, neutral substances, insoluble in water, but soluble in alcohol, and form salts in the absence of water; some of them may be distilled without change. **Azo-benzene** itself (**benzene-azo-benzene**,  $C_6H_5 \cdot N : N \cdot C_6H_5$ ) crystallizes in large red plates, melts at  $68^\circ$ , and distils at  $293^\circ$ . Oxidizing agents convert them into azoxy-, and reducing agents, e.g. phenylhydrazine in the cold, into hydrazo- or amino-compounds. Chlorine and bromine act as substituents.

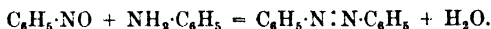
The so-called "mixed" azo-compounds, which contain both an aliphatic and an aryl radical, are also known, e.g. **azo-phenyl-ethyl**,  $C_6H_5 \cdot N : N \cdot C_2H_5$ , a bright-yellow oil (B., 1897, 793).

**Modes of Formation.**—1. By the cautious reduction of nitro- or azoxy-compounds, e.g. by means of sodium amalgam or of an alkaline solution of stannous oxide (B., 1885, 2912). 2. By distilling azoxy-benzene with iron filings. 3. By the oxidation

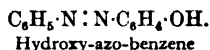
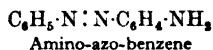
of hydrazo-benzene. 4. By the oxidation of amino-compounds, e.g. together with azoxy-compounds by means of  $\text{KMnO}_4$ :



5. By the action of nitroso- upon amino-compounds in presence of acetic acid. In this way azo-benzene is obtained from nitroso-benzene and aniline acetate:



Amino- and hydroxy-derivatives of azo-benzenes are known, thus:



The former are at the same time bases and azo-compounds, and the latter azo-compounds and phenols (i.e. weak acids).

#### 4. $\beta$ -ARYL-HYDROXYLAMINES

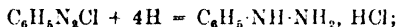
**$\beta$ -Phenyl-hydroxylamine**,  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{OH}$ , is formed when nitro-benzene is reduced with zinc dust and water in the presence of a mineral salt, e.g.  $\text{CaCl}_2$ , or in 80 per cent yield by reducing the nitro-compound in neutral media with hydrogen at room temperature in presence of palladized animal charcoal (B., 1922, 875). It is a colourless crystalline substance melting at  $81^\circ$ , and is relatively unstable. Aqueous solutions rapidly undergo oxidation on exposure to the air, yielding azoxy-benzene; oxidizing agents generally yield nitroso-benzene. Mineral acids immediately cause molecular rearrangement into *p*-amino-phenol,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{OH}$  (cf. Chap. XXXVIII). All the arylated  $\beta$ -hydroxylamines reduce *Fehling's* solution, and this affords a test for an aromatic nitro-compound. If, after warming with water and zinc dust, a solution is obtained which reduces *Fehling's* solution, the presence of a nitro-group in the original compound can be inferred.

### D. Hydrazines

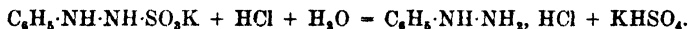
The aromatic hydrazines (*E. Fischer*) correspond with those of the fatty series (cf. p. 124). Phenyl-hydrazine,  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{NH}_2$ , *s*-diphenyl-hydrazine or hydrazo-benzene,  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{NH}\cdot\text{C}_6\text{H}_5$ ;

unsym.-diphenyl-hydrazine,  $(C_6H_5)_2N \cdot NH_2$ , and phenylmethyl-hydrazine,  $(C_6H_5)(CH_3)N \cdot NH_2$ , are all known.

**Phenyl-hydrazine**,  $C_6H_5 \cdot NH \cdot NH_2$ , forms a colourless crystalline mass, melting at  $23^\circ$  to a colourless oil, which quickly becomes brown from oxidation, and which is best distilled under reduced pressure. When kept or when heated it undergoes slow decomposition (*Chattaway*). It forms salts with mineral acids, e.g. the **hydrochloride**,  $C_6H_5N_2H_3$ , HCl (plates). Like all hydrazines, it has strong reducing power, reducing *Fehling's* solution even in the cold. It is readily destroyed by oxidation (*Chattaway*, C. N., 1911, **103**, 217), but is stable towards mild reducing agents. Energetic reducing agents convert it into aniline and ammonia. Gentle oxidation of the sulphate by means of HgO converts it into benzene-diazonium sulphate. It is *prepared*: (a) by reducing benzene-diazonium chloride with the calculated quantity of  $SnCl_2$  and HCl:



(b) by reducing potassium diazo-benzene-sulphonate,  $C_6H_5 \cdot N : N \cdot SO_3K$  (from  $C_6H_5N_2Cl$  and  $K_2SO_3$ ), with zinc dust and acetic acid to potassium phenyl-hydrazine-sulphonate,  $C_6H_5 \cdot NH \cdot NH \cdot SO_3K$ , which is then hydrolysed to phenyl-hydrazine and sulphuric acid:



Alkyl and acyl derivatives of phenyl-hydrazine are known; the former (mono-alkylated derivatives only) are obtained by the action of alkyl iodides on the base or its metallic derivatives. **Phenyl-methyl-hydrazine**, which can be obtained in this way, is largely used for differentiating ketoses and aldoses (p. 339); its constitution follows from its formation by the

reduction of nitroso-methyl-aniline, 
$$\begin{array}{c} C_6H_5 \\ CH_3 \end{array} \rangle N \cdot NO.$$
 Both mono-

and diacyl derivatives are known. The mono-acyl derivatives or **hydrazides** (cf. Amides, Anilides) are obtained by the action of the acid or acid anhydrides on the base; they give a violet-red coloration with sulphuric acid and dichromate of potash, and can be used for isolating acids which are readily soluble; e.g. **acetylphenyl-hydrazide**,  $C_6H_5 \cdot NH \cdot NH \cdot CO \cdot CH_3$ ; m.-pt.  $128^\circ$ .



The base is an important and often an exceedingly delicate reagent for aldehydes and ketones (cf. pp. 149 and 160), as most of the phenyl-hydrazone are solid and crystalline, and are therefore eminently suited for the recognition of aldehydes and ketones. With certain sugars it yields phenyl-hydrazone, but with an excess of the base, osazones (p. 339) are formed. Diketones, keto-aldehydes, &c., also yield osazones.

The phenyl-hydrazone derived from aldehydes readily react with *Grignard* reagents, forming additive compounds at the C:N link. Alkyl unites with C and MgBr with N, so that  $\text{EtCH:N}\cdot\text{NPh} + \text{MgPhBr}$  yields the same product as  $\text{PhCH:N}\cdot\text{NPh} + \text{MgEtBr}$ , viz.  $\text{CHPhEt}\cdot\text{N}(\text{MgBr})\cdot\text{NPh}$ , which with acids gives  $\text{CHPhEt}\cdot\text{NH}\cdot\text{NPh}$ , a *s*-aliphyl-aryl-hydrazine (C. R., 1937, 204, 1262). *Grignard* reagents, on the other hand, react with keto-phenyl-hydrazone, yielding, where possible,  $\alpha$ -alkylated indoles (*ibid.* 502).

With ethyl aceto-acetate, phenyl-hydrazine forms pyrazole derivatives, e.g. phenyl-methyl-pyrazolone, the methyl derivative of which is antipyrine (Chap. XLII, A.).

**Diphenyl-hydrazine**,  $(\text{C}_6\text{H}_5)_2\text{N}\cdot\text{NH}_2$ , is an oily base which boils without decomposition, and, like phenyl-hydrazine, is easily oxidized; it only reduces *Fehling's* solution, however, when warmed. It is obtained by reducing diphenyl-nitrosamine,  $(\text{C}_6\text{H}_5)_2\text{N}\cdot\text{NO}$ , with zinc dust and acetic acid. M.-pt.  $34^\circ$ . Like phenyl-hydrazine, it yields characteristic hydrazones and osazones with the sugars.

***p*-Bromo-phenyl-hydrazine**,  $\text{C}_6\text{H}_4\text{Br}\cdot\text{NH}\cdot\text{NH}_2$ , ***p*-nitro- and 2:4-dinitro-phenyl-hydrazine** are often used in isolating and detecting carbonyl compounds, as the hydrazones crystallize well (B., 1899, 1806; J. C. S., 1922, 717; 1931, 757; J. A. C. S., 1930, 2957).

**Bis (methyl-hydrazine-phenyl) methane**,  $\text{CH}_2(\text{C}_6\text{H}_4\cdot\text{NMe}\cdot\text{NH}_2)_2$ , is recommended as a reagent for characterizing aldehydes, as it reacts only slowly with ketones, with the exception of  $\alpha$ -ketonic acids. (Braun, B., 1908, 2169; Harries, Abs., 1917, i, 210.)

**Tetra-alkyl-hydrazines**,  $\text{R}_2\text{N}\cdot\text{NR}_2$ , are formed by the oxidation of secondary amines with lead dioxide. Many of them dissolve in benzene, giving coloured solutions, which it is presumed contain free radicals,  $\cdot\text{NR}$ , together with tertiary amines,  $\text{NR}_3$  (cf. Chap. LII, B3). The existence of the free radical is supported by the fact that when kept for some time

the chief products are tertiary amines and azo-derivatives,  $RN:NR$ . Tri-phenyl-hydrazine in boiling xylene gives diphenylamine and  $NPh$ , which polymerizes to azo-benzene (*Wieland*). The spontaneous decomposition of hydrazo-benzene (p. 458) into aniline and azo-benzene is a unimolecular reaction, and probably consists in the dissociation into aniline and  $:NPh$  and the polymerization of the latter to azo-benzene (*Stieglitz and Curme*, B., 1913, 911; cf. *Wieland*, *ibid.* 1915, 1094).

### E. Azo-dyes

A number of compounds derived from azo-benzene and its homologues are largely used as dyes, under the name of azo-dyes. These compounds are either basic and contain  $NH_2$  or  $N(CH_3)_2$  groups, or are acidic and then contain either phenolic,  $OH$ , or sulphonic,  $SO_2 \cdot OH$ , and phenolic groups. Azo-benzene itself is a highly-coloured substance, but is not a dye. In order that a coloured substance shall be a dye, it is essential that the colour it imparts to a fabric shall not be removed by washing or treatment with soap. According to *O. Witt*, when certain characteristic groups known as **chromophores**, among which are  $\cdot N:N$  and  $NO_2$ , are present, the compound is coloured or is a **chromogene**; and when, in addition to the chromophore, a strongly basic (e.g.  $NH_2$ ) or acidic group (e.g.  $\cdot OH$  or  $\cdot SO_2 \cdot OH$ ) is also present, we obtain a **dye**, e.g.:

Chromogenes	Dyes
Nitro-benzene	Nitraniline, $NO_2 \cdot C_6H_4 \cdot NH_2$ ;
Nitro-benzene	Picric acid, $(NO_2)_3 \cdot C_6H_3 \cdot OH$ ;
Azo-benzene	<i>p</i> -Hydroxy-azo-benzene, $C_6H_5 \cdot N:N \cdot C_6H_4 \cdot OH$ .

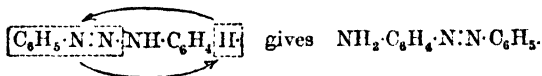
The majority of dyes, when reduced, yield colourless compounds—**leuco-compounds**—which on oxidation are converted into the original dyes.

With regard to the theory of the process of dyeing fabrics, there are still two distinct schools. According to one, the process consists in the formation of definite compounds of the basic or acidic dye with acidic or basic constituents of the fabric dyed. According to the other, the operation is largely a physical one, and the dyed fabric may be regarded as a solid solution.

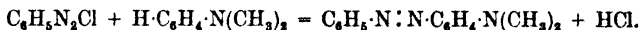
In most cases, silk and woollen—and in a few cases cotton—fabrics can be dyed by direct immersion in a solution of the

dye; but, as a rule, cotton will not dye directly, but requires previous treatment with a **mordant**. The object of the mordant is to deposit some substance on the fabric which will afterwards combine with or fix the dye. The chief mordants employed for acid dyes are the feeble bases aluminium, chromium, or ferric hydroxides, obtained by immersing the fabric in a solution of the metallic acetate, and then subjecting to the action of steam. The product formed by the action of the dye on the mordant is known as a **lake**, and the same dye can give rise to different-coloured lakes according to the mordant used. When basic dyes are employed for cotton goods, the fabric is usually mordanted with tannic acid. Stannic hydroxide obtained from such a salt as  $(\text{NH}_4)_2\text{SnCl}_6$  is also used as a mordant. The lakes are mostly co-ordination compounds (Chap. XLVI, B).

**p-Amino-azo-benzene** is the parent substance of the dyes known as **chrysoidines**. It may be obtained (1) by nitrating azo-benzene and then reducing (this indicates its constitution as an amino-derivative of azo-benzene); (2) by molecular rearrangement of diazo-amino-benzene (p. 456):

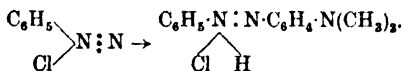


Substituted amino-azo-benzenes, e.g. dimethyl-amino-azo-benzene, are obtained directly by the action of a diazonium salt on a tertiary amine:



For influence of substituents on formation of amino-azo-compounds cf. *Morgan and Micklethwait*, J. C. S., 1907, 370.

Assuming the *Blomstrand* formula for the diazonium salt, the reaction is probably first additive, and then HCl is eliminated:



The azo-group always takes up the *p*-position with respect to the substituted amino-group if this position is free. If, however, the *p*-position is already substituted, a dye is not formed, or is formed very incompletely, and the *o*-position is taken up.

The chrysoidines are coloured yellow to brown, and, as they contain amino- or substituted amino-groups in the molecule, are basic, and form well-defined salts with mineral acids.

Among the simplest chrysoidines are:

**Aniline yellow**, the hydrochloride of *p*-amino-azo-benzene. It is now very little used. Its sulphonic acid is **acid yellow**.

**Butter yellow**, from diazotized aniline and dimethylaniline, is used for coating windows of dark rooms.

**Chrysoidine**, or 2 : 4-diamino-azobenzene hydrochloride,  $C_6H_5 \cdot N:N \cdot C_6H_3(NH_2)_2$ ,  $H^+ [N_2:(NH_2)_2 = 1:2:4]$ , dyes silk and wool directly an orange-red colour.

**Bismark brown**, obtained by diazotizing *m*-phenylenediamine and coupling the tetrazonium salt with more of the base, is a mixture of hydrochlorides of dis- and mono-azo-derivatives.

The brown coloration obtained by the addition of a few drops of dilute nitrous acid solution to *m*-phenylenediamine is due to the formation of Bismarck brown or a related substance. The hydrochloride crystallizes in reddish-brown plates.

Many of the chrysoidine dyes are sulphonated derivatives of amino-azo-benzene, e.g. **methyl orange**, the sodium salt of **helianthine** or *p*-dimethamino-azo-benzene-*p*-sulphonic acid,  $(CH_3)_2N \cdot C_6H_4 \cdot N:N \cdot C_6H_4 \cdot SO_2 \cdot OH$ . It is largely made use of as an indicator in volumetric analysis, as it is not affected by weak acids, e.g. carbonic, but is an extremely delicate reagent for the feeblest alkalis.

It is highly probable that the sodium salt has the azo-structure, but on liberating the acid it tautomerizes to  $\bar{O}:O_2S \cdot C_6H_4 \cdot NH \cdot N:C_6H_4:NMe_2$ , and hence the distinct change in colour.

**Orange IV** is the corresponding diphenyl compound,  $NPh_2 \cdot C_6H_4 \cdot N:N \cdot C_6H_4 \cdot SO_3Na$ , and is obtained from diazotized sulphanilic acid and diphenylamine. It is used for dyeing animal fibres.

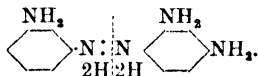
The dyes known as **tropæolines** are derivatives of *p*-hydroxy-azo-benzene. Such compounds are obtained by adding the cold diazotized solution to an *alkaline* solution of a phenol. The dye is then salted out by the addition of sodium chloride and collected. The reaction is often made use of in testing for a primary aromatic amine (p. 452), as the precipitates produced are usually coloured bright red. The azo-group invariably occupies the *p*-position with respect to the OH group, unless

this is already substituted. With a *p*-alkylated phenol the azo-group takes the *o*-position, whereas with  $\cdot\text{CO}_2\text{H}$  or  $\cdot\text{SO}_3\text{H}$  *p*- to OH these groups are displaced by the azo-group.

***p*-Hydroxy-azo-benzene** crystallizes in brick-red prisms, and is a yellowish-red dye.

**Resorcin yellow**,  $\text{OH}\cdot\text{SO}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{N}\cdot\text{C}_6\text{H}_3(\text{OH})_2$ , 2:4-dihydroxy-azo-benzene-4'-sulphonic acid, obtained by coupling a diazotized solution of sulphanilic acid with an alkaline solution of resorcinol, is known as Tropæolin O.

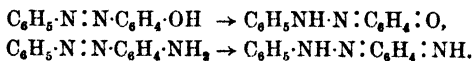
The constitution of an azo-dye can usually be determined by an examination of its decomposition products, especially the products formed by energetic reduction; e.g. Bismarck brown, on reduction with tin and hydrochloric acid, yields a mixture of 1:3-diamino- and 1:2:4-triamino-benzene:



**Bis-azo-dyes.**—Certain well-known dyes, e.g. **Biebrich scarlet**, contain two azo-groups. Such can be obtained by diazotizing an amino-derivative of azo-benzene, and then coupling with a tertiary amine or with a phenol, yielding a compound of the type  $\text{C}_6\text{H}_5\cdot\text{N}:\text{N}\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{N}\cdot\text{C}_6\text{H}_4\cdot\text{OH}$ .

Another type of bis-azo-compound is formed by coupling a diamine or dihydric phenol with 2 mols. of a diazonium salt, especially when the two OH groups are in the *m*-position.

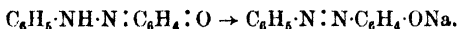
Many amino- and hydroxy-azo-derivatives react as tautomeric substances, especially those which contain an  $\text{NH}_2$  or OH group in the ortho-position with respect to the  $\text{N}_2$  radical. These react as though they were quinone hydrazones or quinone-imide derivatives, e.g.:



For a general summary compare *Auwers* (A., 1908, 360, 11) and *Smith and Mitchell* (J. C. S., 1908, 842; 1909, 1430). The general conclusion drawn is that all the compounds, both *para* and *ortho*, are true hydroxy-azo-compounds.

According to *Hantzsch*, many of the hydroxy-azo-compounds are pseudo-acids (p. 425), i.e. the hydrogen compound is the

quinone hydrazone; but in the formation of a salt, intramolecular rearrangement occurs, e.g.:



For further types of azo-dyes cf. Chap. LIX, B.

## F. Phosphorus Compounds, &c.; Organo-Metallic Derivatives

The phosphorus, &c., compounds of the fatty series have their analogues in corresponding compounds of the aromatic; these latter have been investigated by *Michaelis* and his pupils (A., 181, 188, 201, 212, and 229; B., 28, 2205): for instance, **phenyl phosphine**,  $\text{C}_6\text{H}_5\cdot\text{PH}_2$ ; **phenyl phosphinic acid**,  $\text{C}_6\text{H}_5\text{PO}(\text{OH})_2$ ; **phosphenyl chloride**,  $\text{C}_6\text{H}_5\cdot\text{PCl}_2$ ; **phosphino-benzene**,  $\text{C}_6\text{H}_5\text{PO}_2$ ; and **phospho-benzene**,  $\text{C}_6\text{H}_5\text{P}:\text{P}\cdot\text{C}_6\text{H}_5$  (these two last being analogous to nitro- and to azo-benzene). Some of those compounds are solid, and they are less volatile and more stable than the corresponding aliphatic compounds. For important arsenic compounds see Chap. LXVI.

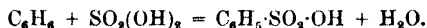
**Aromatic Organo-Metallic Compounds.**—Mercury, tin, lead, tellurium, and magnesium yield phenyl derivatives. **Mercury phenyl**,  $\text{Hg}(\text{C}_6\text{H}_5)_2$ , is obtained by the action of sodium amalgam on bromobenzene. It is relatively stable. Numerous compounds of the type of **phenyl magnesium bromide**,  $\text{C}_6\text{H}_5\cdot\text{Mg}\cdot\text{Br}$ , have been prepared, and are used as synthetical reagents (cf. p. 416).

## XXIII. AROMATIC SULPHONIC ACIDS

The aromatic sulphonic acids are very similar in properties to the sulphonic acids of the fatty series, but can be obtained much more readily. One of the characteristic properties of benzene and its derivatives is the readiness with which they react with concentrated sulphuric acid, yielding sulphonic acids. Alkylated benzenes are sulphonated more readily

than benzene. When several methyl groups are present anomalies are observed, e.g.  $C_6HMe_5$  on sulphonation gives a mixture of  $C_6Me_6$  and  $C_6HMe_4 \cdot SO_3H$  (Smith and others, J. A. C. S., 1929, 2994; 1932, 1614). In some cases fuming sulphuric acid is used; in other sulphuryl chloride,  $OH \cdot SO_2 \cdot Cl$ .

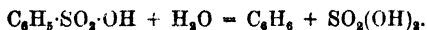
**Benzene-sulphonic acid**,  $C_6H_5 \cdot SO_2 \cdot OH$  (Mitscherlich, 1834), is formed when benzene is heated with concentrated sulphuric acid for some hours:



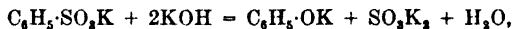
As in the case of ethyl hydrogen sulphate, advantage is taken of the solubility of its barium, calcium, or lead salt to separate it from the excess of sulphuric acid; or its sodium salt is separated by the addition of sodium chloride.

It crystallizes in small plates containing  $1\frac{1}{2}H_2O$ , deliquesces in the air, and is readily soluble in alcohol. The barium salt crystallizes in glistening mother-of-pearl plates containing  $1H_2O$ .

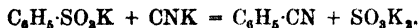
It is very stable, and is not hydrolysed when boiled with alkalis or acids (cf. Ethyl hydrogen sulphate). It is, however, decomposed into benzene and sulphuric acid when heated with hydrochloric acid at  $150^\circ$ , or with water vapour at a high temperature (cf. p. 407):



When fused with alkali, it yields phenol in the form of its potassium salt:

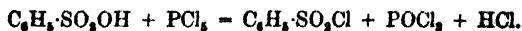


and when distilled with potassium cyanide, it yields benzonitrile:



When the K salt is fused with potassium formate  $\cdot SO_3K$  is replaced by  $\cdot CO_2K$ . Direct replacement of  $SO_3H$  by halogen occurs readily when an  $NH_2$  or  $OH$  group is *o* or *p* to the  $SO_3H$  group, e.g. sulphanilic acid ( $NH_2$  *p* to  $SO_3H$ ) readily give *s*-tribromaniline with excess of bromine water.

With  $PCl_5$  the  $OH$  group present in the sulphonic acid radical is replaced by chlorine, and **benzene-sulphonic chloride** is formed:

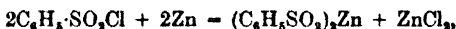


This is an oil, insoluble in water; it melts at  $14.5^{\circ}$ , and boils at  $120^{\circ}$  (under 10 mm. pressure); as an acid chloride it is reconverted into sulphonic acid when boiled with water. The sulphonic or sulphonyl chlorides are relatively more stable than the acyl chlorides, and some can be distilled with water, but all are hydrolysed by alkalis. When boiled with alcohol the chlorides yield esters, and with ammonia compounds of the type **benzene-sulphonamide**,  $C_6H_5 \cdot SO_2 \cdot NH_2$  (lustrous mother-of-pearl plates melting at  $150^{\circ}$ ). This compound can be sublimed, and corresponds with other amides in its properties. The amido-group, however, is so affected by the strongly acylous  $SO_2$  group that its hydrogen is replaceable by metals, and the sulphonamides consequently *dissolve in aqueous solutions of alkali hydroxides*.

The sulphonamides are largely made use of in distinguishing the various sulphonic acids. These acids themselves are difficult to purify, as a rule do not crystallize well, and have no definite melting-point. The sulphonamides, on the other hand, crystallize readily, and have sharp melting-points. The sodium salt of the acid is treated with  $PCl_5$ , and the chloride thus obtained is warmed with ammonium carbonate.

Benzene-sulphonic chloride likewise yields sulphonamides with primary and secondary amines,  $C_6H_5 \cdot SO_2 \cdot NHR$  and  $C_6H_5 \cdot SO_2 \cdot NRR'$ , the former of these being soluble in alkali, but the latter insoluble. Tertiary amines do not, of course, give sulphonamides. This serves as the basis of a method for separating primary, secondary, and tertiary bases, especially when  $\beta$ -anthraquinone sulphonic chloride is used (*Hinsberg*, B., 1890, 2962; 1900, 477, 557, 3526; 1905, 906).

Benzene-sulphonic chloride in alcoholic or ethereal solution, treated with zinc dust, yields zinc benzenesulphonate:



whereas more vigorous reducing agents, e.g. zinc mineral acid, yield thiophenols.

**Benzene-sulphinic acid** crystallizes in large glistening prisms, readily soluble in hot water, alcohol, and ether. It possesses reducing properties, and is itself readily reduced to thiophenol:



Thio-phenols can also be obtained by reducing the sulphonamides derived from primary arylamines or the arylsulphonic



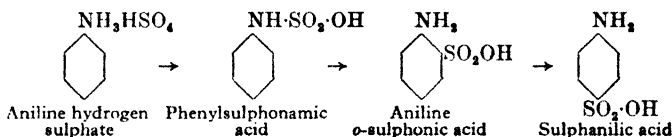
chlorides with HI and  $\text{PH}_4\text{I}$ . The sulphonic acids and their esters cannot be reduced by this method.

Sulphinic acids can be synthesized from *Grignard* reagents and  $\text{SO}_2$ .

Numerous substituted sulphonic acids are known.

The **nitro-benzene-sulphonic acids**,  $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_3\text{H}$ , are obtained by nitrating benzene-sulphonic acid or by sulphonating nitro-benzene, the *m*-compound preponderating. Reducing agents convert them into the—

**Amino-benzene-sulphonic acids**,  $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_3\text{H}$ . The *p*-compound, which is termed **sulphanilic acid**, is obtained by heating aniline sulphate at  $180^\circ$ – $200^\circ$  (*Gerhardt*, 1845); also by reducing *p*-nitro-benzene-sulphonic acid. The conversion of aniline sulphate into sulphanilic acid proceeds as follows:



(Cf. *Bamberger*, B., 1897, 2274.) It crystallizes in rhombic plates (+  $\text{H}_2\text{O}$ ), sparingly soluble in water, forms metallic salts, e.g. **sodium sulphanilate**,  $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_3\text{Na} + 2\text{H}_2\text{O}$  (large plates), but does not combine with acids. The formula

$\text{C}_6\text{H}_4 \begin{array}{c} \text{NH}_2 \\ \diagup \quad \diagdown \\ \text{SO}_3 \end{array}$  possibly expresses the constitution of sulph-

anilic acid. The *m*-acid, also termed **metanilic acid**, is employed in the preparation of azo-dyes, e.g. metaniline yellow; it crystallizes in fine needles or prisms.

An  $\text{SO}_3\text{H}$  group can usually be replaced by H when the acid is heated under pressure with a mineral acid and the readiness depends upon the presence of other groups, e.g. *o* and *p* OH and  $\text{NH}_2$  groups.

**Diazo-benzene-sulphonic acid**,  $\text{C}_6\text{H}_4 \begin{array}{c} \text{N}:\text{N} \\ \diagup \quad \diagdown \\ \text{SO}_3 \end{array}$  (the anhydride of  $\text{C}_6\text{H}_4 \begin{array}{c} \text{N}:\text{N}\cdot\text{OH} \\ \diagup \quad \diagdown \\ \text{SO}_3\text{H} \end{array}$ ), is obtained by adding a mixture of sul-

phanilate and nitrite of sodium to dilute sulphuric acid. It forms colourless needles, sparingly soluble in water, shows all

the reactions of the diazo-compounds, and is of great importance for the preparation of azo-dyes.

**Benzene-disulphonic acids**,  $C_6H_4(SO_3H)_2$  (principally meta-), and **benzene-trisulphonic acids**,  $C_6H_3(SO_3H)_3$ , result from the energetic sulphonation of benzene with fuming sulphuric acid. The 3 isomeric disulphonic acids yield dinitriles  $C_6H_4(CN)_2$  when distilled with KCN and the *m*-compound yields resorcinol when fused with KOH.

Almost all the homologues of benzene, with the exception of hexamethyl-benzene, yield sulphonic acids. From toluene are obtained the *o*-, *m*-, and *p*-toluene sulphonic acids,  $CH_3 \cdot C_6H_4 \cdot SO_3H$  (*Holleman* and *Caland*, B., 1911, 2504). Of these it is the *p*-acid which is formed in largest quantity directly; its potassium salt crystallizes beautifully.

The sulphonic acids of the three xylenes, the **xylene-sulphonic acids**,  $C_6H_3(CH_3)_2SO_3H$ , serve for the separation of these isomers from each other; and the power of crystallization of the salts or amides of the sulphonic acids of the higher benzene homologues is frequently made use of for the recognition and separation of these hydrocarbons.

The N-halogenated sulphonamides have received much attention. The compounds  $C_6H_5 \cdot SO_2 \cdot NCl \cdot CH_3$  and  $C_6H_5 \cdot SO \begin{smallmatrix} \diagup OK \\ \diagdown NCl \end{smallmatrix}$  were prepared by *Chattaway* (J. C. S., 1905, 145), the former by the action of hypochlorous acid on the corresponding amide and the latter by the action of warm potassium hydroxide on the dichloride,  $C_6H_5 \cdot SO_2 \cdot NCl_2$ , obtained from the amide and hypochlorous acid (cf. Chap. LXV, A5, Antiseptics).

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## XXIV. PHENOLS

The hydroxylic derivatives of benzene and its homologues are usually divided into (a) phenols and (b) aromatic alcohols. The phenols all contain the hydroxyl group or groups directly attached to the benzene nucleus, e.g.  $C_6H_5(OH)$ ,  $C_6H_4(OH)_2$ , whereas in the alcohols the hydroxyl group is present in a side chain, e.g.  $C_6H_5 \cdot CH_2 \cdot OH$ .

One important point of difference between the phenols and alcohols is the more pronouncedly acidic nature of the phenol. The aromatic alcohols closely resemble those of the aliphatic series, but the phenols react as feeble acids, the hydroxylic hydrogen being displaced by the action of sodium or potassium hydroxide.

The phenols are either liquid or solid compounds, and are often characterized by a peculiar odour, e.g. carbolic acid and thymol. Most of them can be distilled without decomposition, and all are readily soluble in alcohol or ether; some dissolve easily in water, others less readily, the solubility tending to increase with the number of hydroxyl groups present in the molecule. Many of them are antiseptics, e.g. phenol, creosol, thymol, and resorcinol.

The phenols are usually divided into mono-, di-, tri-, or tetrahydric, according to the number of OH groups present in the molecule.

*Behaviour.*—1. Like the alcohols, the phenols are capable of forming **ethers** such as anisole,  $C_6H_5 \cdot O \cdot CH_3$ , **esters**, e.g. phenyl acetate,  $C_6H_5 \cdot O \cdot CO \cdot CH_3$ , and phenyl hydrogen sulphate,  $C_6H_5 \cdot O \cdot SO_2 \cdot OH$ , **thio-compounds**, e.g. thiophenol,  $C_6H_5 \cdot SH$ , &c.

They can only be compared with the tertiary alcohols, since they cannot, like the primary or secondary alcohols, yield acids or ketones containing an equal number of carbon atoms in the molecule upon oxidation.

2. The phenols are weak acids, and form salts known as **phenates** or **phenoxides**, e.g.  $C_6H_5 \cdot OK$ , potassium phenate or potassium phenoxide; most of the salts are readily soluble in water, and far more stable than the alcoholates, with which they correspond.

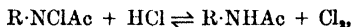
In aqueous solutions the salts are largely hydrolysed, and are decomposed by carbon dioxide, as the phenols are extremely feeble acids comparable with hydrocyanic acid. The acid character of the phenols is considerably increased by the presence of acylous groups, especially  $NO_2$ , in the molecule (see Picric Acid).

3. The presence of  $NH_2$ , or OH groups in the benzene nucleus renders compounds much more reactive towards halogens, nitric acid, sulphuric acid, oxidizing agents, &c. With polyamines and aminophenols the reactivity is such that the compounds undergo spontaneous oxidation on exposure to the air. The reactivity with chlorine is so great that frequently

# MONOHYDRIC PHENOLS

Formula	Name	Positions of Substituents OH in 1	Melting-point	Boiling-point	Specific gravity
$C_6H_5 \cdot OH$	Phenol ..	—	42.5°	183°	1.039
$CH_3 \cdot C_6H_4 \cdot OH$	<i>o</i> -Cresol ..	1:2	30	191	1.043
	<i>m</i> -Cresol ..	1:3	4	203	1.035
	<i>p</i> -Cresol ..	1:4	36	202	1.034
$(CH_3)_2C_6H_3 \cdot OH$	adj.- <i>o</i> -Xylenol ..	1:2:3	73	213	—
	asym.- <i>o</i> -Xylenol ..	1:3:4	65	222	—
	<i>p</i> -Xylenol ..	1:2:5	75	209	—
$(CH_3)_3C_6H_2 \cdot OH$	Pseudo-cumenol ..	1:2:4:5	73	234	—
$(CH_3)_2CH \cdot C_6H_3(CH_3)(OH)$	Carvacrol ..	1:2:4	0.5	237	0.979
	Thymol ..	1:3:6	51	232	0.982
$C_6H_5(OH)(OMe)(CH_2 \cdot CH \cdot CH_2)$	Eugenol ..	1:2:4	—	252	1.070
$C_6H_4(OH)_2$	Catechol ..	1:2	104	240	—
	Resorcinol ..	1:3	119	276	—
	Quinol ..	1:4	169	—	—
$CH_3 \cdot C_6H_3(OH)_2$	Orcinol ..	1:3:5	107	288	—
TRIHYDRIC PHENOLS					
$C_6H_3(OH)_3$	Pyrogallol ..	1:2:3	132	—	—
	Hydroxyquinol ..	1:2:4	140	—	—
	Phloroglucinol ..	1:3:5	217-219	—	—

compounds of this type cannot be chlorinated by the usual methods. *Orton and King* (J. C. S., 1911, 1185; 1927, 986; 1928, 998; 1930, 37) have introduced a method based upon the fact that the reversible reaction,



proceeds from left to right in the presence of glacial acetic acid, and thus by taking very dilute solutions of hydrochloric acid, e.g. 0.021 *N*, the concentration of the chlorine is kept so low that chloro-derivatives are obtained free from products of oxidation. Cresols can be chlorinated in the same manner. The acetyl derivative generally used is 2:4-dichloro-acetyl-chloranilide, and if the theoretical amount of this compound is used the reaction proceeds to completion, as hydrogen chloride is formed by the action of the chlorine on the amine or phenol.

The method has been used for determining the velocities of many chlorinations (J. C. S., 1928, 782, 1006, 3073).

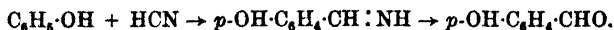
4. Many phenols give characteristic colorations with ferric chloride in neutral solution, e.g. phenol and resorcinol violet, catechol green, and orcinol blue-violet; while pyrogallol yields a blue colour with ferrous sulphate containing a ferric salt, and a red one with ferric chloride. Bleaching-powder and iodine solution, in certain cases, also give particular coloration.

5. *Liebermann's Reaction*.—When the phenols are mixed with concentrated  $H_2SO_4$  and a drop of nitrite solution or of a nitrosamine, they yield intensely coloured solutions which turn to a deep-blue or green when diluted and rendered alkaline with potash.

6. The sodium and potassium salts of the phenols react with  $CO_2$  (*Kolbe*) or with  $COCl_2$ , with formation of aromatic hydroxy-acids, e.g. salicylic acid (Chap. XXVI, A3).

7. The phenols couple with diazonium salts to form azo-dyes (Chap. XXII, E.); heated with benzo-trichloride,  $C_6H_5 \cdot CCl_3$ , they yield the aurin dyes, and with phthalic acid, phthaleins (Chap. XXX, A3).

8. The phenols condense with HCN in the presence of mineral acid yielding *aldimines* which can be readily hydrolysed to hydroxy-aldehydes:



9. When heated with zinc dust, the phenols are converted into the corresponding hydrocarbons (*Baeyer*).

10. When heated with the additive compounds of zinc chloride and ammonia or calcium chloride and ammonia, the OH is replaced by  $\text{NH}_2$  (Chap. XXI, A.).

11. Heating with phosphorus pentachloride partially converts the phenols into chlorinated hydrocarbons, and heating with  $\text{P}_2\text{S}_5$  into thio-phenols.

*Occurrence.*—Many individual phenols are found in the vegetable and animal kingdoms. They are also present in the tars from gas-works, coke ovens, and low-temperature distillation plants.

*Constitution.*—The hydroxyl-groups in phenol,  $\text{C}_6\text{H}_5\cdot\text{OH}$ , and in the di- and polyhydroxy-benzenes, containing six carbon atoms, are linked to the benzene nucleus. That this is also the case in the homologues of these compounds follows: (a) from their completely analogous reactions; (b) from their behaviour upon oxidation. Thus, when oxidized, *m*-cresol yields *m*-hydroxy-benzoic acid, and hence the OH is present in the benzene nucleus and not in the side chain, and must be in the *m*-position with respect to the methyl group.

## A. Monohydric Phenols

*Modes of Formation.*—1. Many phenols are formed during the destructive distillation of the more complex carbon compounds, especially of wood and coal; they are therefore present in wood- and coal-tars. Ordinary coal-tar contains phenol, the cresols, &c., and wood-tar, the methyl ethers, e.g. guaiacol,  $\text{C}_6\text{H}_4\cdot(\text{OH})(\text{O}\cdot\text{CH}_3)$ , and its homologue creosol,  $\text{C}_8\text{H}_3(\text{CH}_3)(\text{OH})(\text{O}\cdot\text{CH}_3)$ .

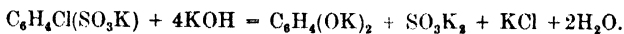
The phenols are isolated from coal-tar, &c., by shaking with sodium hydroxide solution, in which they dissolve, saturating the alkaline solution with hydrochloric acid, and purifying the precipitated phenols by fractional distillation.

2. Phenols are formed together with an alkali sulphite when salts of sulphonic acids are fused with potassium or sodium hydroxides (*Kekulé, Wurtz, Dusart, 1867*):



In the laboratory nickel or silver basins are used for this fusion, and on the large scale iron boilers, &c. The alkali salts of the phenols are formed, and the free phenols may be liberated, by the addition of mineral acid. The chlorinated

sulphonic acids and the chlorinated phenols also exchange the halogen for hydroxyl when fused with potash:

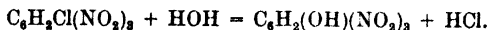


In certain cases, intramolecular rearrangement occurs during this fusion, e.g. all three bromo-benzene-sulphonic acids yield *m*-dihydroxy-benzene (resorcinol) when fused with potash.

3. They are formed when aqueous solutions of diazonium salts are heated (*Griess*; Chap. XXII, A.). As a rule, a very dilute sulphuric acid solution is employed.

Benzene can be oxidized to phenol by ozone or perhydrol, and atmospheric oxygen can bring about oxidation in the presence of alkali or of  $\text{AlCl}_3$ , and hence in the fusion of sodium benzene sulphonate with alkali not only is  $\text{C}_6\text{H}_5\text{ONa}$  formed, but also  $\text{C}_6\text{H}_4(\text{ONa})_2$  or even  $\text{C}_6\text{H}_3(\text{ONa})_3$  if much oxygen is present.

5. The phenols cannot be prepared from chloro-, bromo-, or iodo-benzene in the same way as the alcohols from alkyl chlorides, bromides, or iodides, the halogen being bound too firmly to the benzene nucleus. The bromo-compounds when heated with alkalis under a pressure of 20 atmospheres at about  $300^\circ$ , and the chloro compounds at  $340^\circ$ – $390^\circ$  and high pressure yield metallic phenoxides. If nitro-groups are present in *o*- or *p*-positions, an exchange of this kind can be effected by heating with aqueous sodium or potassium hydroxides; *s*-trinitro-chloro-benzene reacts with water alone:



Similarly, the amino-group in amino-compounds may be replaced by hydroxyl by means of boiling alkalis, provided nitro-groups are also present in certain position; thus *o*- and *p*- (not *m*-) dinitro-aniline yield dinitro-phenols (cf. Chap. XXXVI).

6. Phenols are also formed when salts of the aromatic hydroxy-acids are distilled with lime, or when their silver salts are carefully heated:

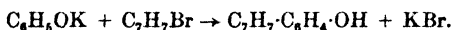


7. Homologues of phenol are readily prepared by reducing certain aromatic hydroxy-ketones or aldehydes with zinc amalgam and HCl. Thus *p*- $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CHO}$  gives *p*- $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$  and *OH}\cdot\text{C}\_6\text{H}\_4\cdot\text{CO}\cdot\text{CH}\_3 gives *OH}\cdot\text{C}\_6\text{H}\_4\cdot\text{CH}\_2\cdot\text{CH}\_3.**

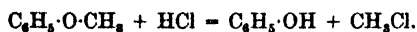
**Phenol**, *Carbolic acid*, *hydroxy-benzene*,  $C_6H_5OH$ , was discovered in 1834 by *Runge* in coal-tar. It occurs in the urine of the herbivora and in human urine as phenyl hydrogen sulphate, also in cocoanut-shell tar, and in bone-oil. It forms long, colourless needles, melts at  $42^\circ$ , boils at  $181^\circ$ , is soluble in fifteen parts of water at  $16^\circ$ , and itself dissolves some water, a small percentage of the latter sufficing to liquefy the crystalline phenol. Alcohol and ether dissolve it readily. It is hygroscopic, and possesses a characteristic odour and burning taste, is poisonous, acts as an efficient antiseptic, and exerts a strongly corrosive action upon the skin. As a very feeble acid it dissolves readily in caustic potash solution, but not in the carbonate. Ferric chloride colours the aqueous solution violet, while a pine shaving moistened with hydrochloric acid is turned greenish-blue by phenol.

**Hexahydro-phenol**, **Cyclohexanol**,  $C_6H_{11}\cdot OH$ , made by the catalytic reduction of phenol, has b.-pt.  $160^\circ$  and is a commercial solvent.

**Phenolic ethers** are usually obtained from an alkali phenoxide and an alkyl bromide in alcoholic solution; in certain cases in benzene solution the product is an ortho substituted phenol, due to the wandering of the alkyl group from O to C of the nucleus. This is especially true when allyl, benzyl, and cinnamyl bromides are used:



**Anisole**, or *Phenyl methyl ether*,  $C_6H_5\cdot O\cdot CH_3$ , and **phenetole**, or *phenyl ethyl ether*,  $C_6H_5\cdot O\cdot C_2H_5$ , are best obtained by heating phenol and caustic soda with methyl or ethyl sulphates or halides; the former is also obtained by distilling anisic acid with lime. They are liquids of ethereal odour which boil at a lower temperature than phenol, just as ether has a lower boiling-point than alcohol. They are very stable neutral compounds, which are not readily hydrolysed by acids or alkalis; when heated with HI to  $140^\circ$ , or with HCl to a higher temperature, or with aluminium chloride, they yield phenol:



When methylating phenols with methyl sulphate better yields are given by using NaOH than by KOH, but for esters potash is preferable (*Klemens*, Mon., 1918, 553).

**Phenyl ether**, *Diphenyl oxide*,  $(C_6H_5)_2O$ , is formed when



phenol is heated with  $\text{ZnCl}_2$  or  $\text{AlCl}_3$ , but not with  $\text{H}_2\text{SO}_4$ . Also by heating  $\text{C}_6\text{H}_5\text{OK}$  with  $\text{C}_6\text{H}_5\text{Br}$  and a little copper powder at  $210^\circ$  (*Ullmann and Spongel, A., 1906, 350, 86*). It crystallizes in needles, and is not decomposed by hydriodic acid (*B., 1923, 176*).

Sodium reacts with di-aryl ethers, forming sodium phenoxide and sodium-phenyl:



With  $\text{CHPh}_2\cdot\text{O}\cdot\text{CH}_3$  the products are  $\text{CH}_3\text{ONa}$  and  $\text{CHPh}_2\cdot\text{Na}$ .

The *p*-nitrobenzyl ethers of phenols are often utilized for characterizing specific phenols as they crystallize well and have definite melting-points (*Reid, J. A. C. S., 1917, 304; 1920, 615*).

**Esters.**—**Phenyl hydrogen sulphate**,  $\text{C}_6\text{H}_5\cdot\text{O}\cdot\text{SO}_2\cdot\text{OH}$  (cf. Ethyl hydrogen sulphate), is only capable of existence in the form of salts, being immediately hydrolysed into phenol and sulphuric acid when attempts are made to isolate it. The **potassium** salt,  $\text{C}_6\text{H}_5\text{O}\cdot\text{SO}_2\cdot\text{OK}$  (plates, sparingly soluble in water), is found in the urine of the herbivora and also in human urine after the consumption of phenol, and it may be prepared synthetically by heating potassium phenate with potassium pyro-sulphate in aqueous solution (*Baumann*). It is very stable towards alkalis, but is hydrolysed by hydrochloric acid.

The acetates, e.g. **phenyl acetate** (b.-pt.  $193^\circ$ ) are readily hydrolysed. As the OH groups increase the reactivity of benzene compounds, it is necessary in certain reactions to protect these groups by (1) acetylation, or (2) conversion into a carbonic ester by the action of ethyl chloroformate. After the reaction the acetyl and carbonate group can be removed by hydrolysis.

Acetyl derivatives of phenols are formed by heating with acetic anhydride and anhydrous sodium acetate or simply by acting on an aqueous solution of the phenoxide at  $0^\circ$  with a slight excess of acetic anhydride.

Benzoyl derivatives are usually obtained by the *Schotten-Baumann* method (p. 515).

The 3:5-dinitro-benzoyl derivatives are used for characterizing phenols (*Helv., 1928, 800*).

**Thio-phenol**, *Phenyl hydrosulphide*,  $\text{C}_6\text{H}_5\cdot\text{SH}$ , is prepared by reducing benzene-sulphonic chloride, or by heating phenol

with  $P_2S_5$ . It is a liquid of most unpleasant odour, and of pronounced mercaptan character (see p. 98). It yields, for instance, a mercury compound,  $(C_6H_5S)_2Hg$ , crystallizing in glistening needles, and also salts with other metals. When warmed with concentrated  $H_2SO_4$ , a cherry-red and then a blue coloration is produced.

Closely related to the above are: (a) **phenyl sulphide**,  $(C_6H_5)_2S$ , which is formed by the action of benzene-diazonium chloride upon thio-phenol:



It is a liquid smelling of leeks, and is oxidizable to **phenyl sulphone**,  $(C_6H_5)_2SO_2$ ; (b) **phenyl disulphide**,  $(C_6H_5)_2S_2$  (glistening needles, m.-pt.  $60^\circ$ ), which is very easily prepared by the action of iodine upon the potassium compound of thio-phenol, or by exposing an ammoniacal solution of the latter to the air. It is readily reduced to thio-phenol, and may be indirectly oxidized to **benzene-disulphoxide**,  $(C_6H_5)_2S_2O_2$ . (Cf. the corresponding compounds of the fatty series, p. 98 *et seq.*)

## 1. SUBSTITUTED PHENOLS

**Chloro- and Bromo-phenols.**—Chlorine and phenol yield *o*- and *p*-chloro-phenols. All three compounds may be obtained by reducing and diazotizing the halogenated nitro-benzenes. Thio-cyanogen in non-aqueous solvents forms the *p*-thiocyano-phenol.

Of the isomeric di-derivatives, the *p*-compounds have the highest melting-point and the *o*- the lowest; thus *o*-chloro- and bromo-phenols are liquid and the *p*-compound solid. When fused with caustic potash they yield dihydroxy-benzenes (this Chap., B.), often with a molecular rearrangement. The chloro-phenols have a sharp, persistent odour. All the 5 nuclear hydrogen atoms of phenol can be replaced by chlorine and bromine.

When an excess of bromine water is added to an aqueous solution of phenol, a precipitate of *s*-tribromo-phenol (colourless needles, melting at  $96^\circ$ ) is obtained.

***p*-Nitroso-phenol**,  $OH \cdot C_6H_4 \cdot NO$ , prepared from phenol and nitrous acid (*Baeyer*), by boiling nitroso-dimethyl-aniline with caustic-soda solution (see p. 440), and by the action of hydroxyl-amine upon quinone, is identical with quinone monoxime,  $O \colon C_6H_4 \colon N \cdot OH$  (Chap. XXV, F.). It crystallizes in fine colourless needles which readily become brown, or in large greenish-brown plates, and detonates when heated.

**Nitro-phenols.**—A mixture of *o*- and *p*-nitro-phenols is obtained when phenol is mixed with cold dilute nitric acid; the *p*-compound preponderates if the liquid is cold, and the ortho- if it is warm. When distilled with steam, the 1 : 2 compound volatilizes, while the 1 : 4 remains behind. *m*-Nitro-phenol is obtained by diazotizing *m*-nitraniline.

The *o*- and *p*-compounds can also be obtained by fusing *o*- and *p*-nitranilines with potash, and *p*-nitro-phenol has been synthesized from nitro-malonaldehyde,  $\text{NO}_2\cdot\text{CH}(\text{CHO})_2$ , and acetone (*Hill and Torray*, B., 1895, 2598).

The *o*-compound crystallizes in yellow prisms, and melts at  $45^\circ$ , the *m*- in yellow crystals, melting at  $96^\circ$ , and the para- in colourless needles, melting at  $114^\circ$ .

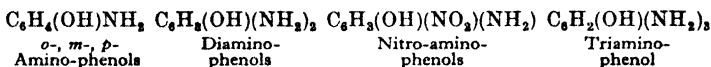
The acid character of phenol is so strengthened by the entrance of the nitro-group that its salts are not decomposed by carbonic acid, but are formed from the nitro-phenols and alkali carbonate. **Sodium *o*-nitro-phenate**,  $\text{C}_6\text{H}_4(\text{NO}_2)\text{ONa}$ , crystallizes in dark-red prisms, and **potassium *p*-nitro-phenate** in golden needles. (For constitution of the salts see Chap. LXXI, D., Absorption Spectra.) Halogens and nitric acid readily substitute further in these mono-nitro-compounds; nitric acid yields two isomeric **dinitro-phenols**,  $\text{C}_6\text{H}_3(\text{NO}_2)_2\text{OH}$  ( $\text{OH}:\text{NO}_2:\text{NO}_2 = 1:2:4$  and  $1:2:6$ , i.e. the two  $\text{NO}_2$  groups are always in the *m*-position to one another). The 2 : 4-dinitro-phenol is made from benzene and nitrous gases in the presence of acetic acid and mercury as catalyst. The yield is good, and the process can be made continuous. Further nitration in the presence of sulphuric acid gives:

**Picric acid**, *s*-Trinitro-phenol,  $\text{C}_6\text{H}_2(\text{NO}_2)_3\cdot\text{OH}$ , ( $\text{OH}:\text{NO}_2:\text{NO}_2:\text{NO}_2 = 1:2:4:6$ ). This compound was discovered in 1799. It may also be prepared by the direct oxidation of *s*-trinitro-benzene with  $\text{K}_3\text{FeC}_6\text{N}_6$ , and is produced by the action of concentrated nitric acid upon the most varied organic substances, e.g. silk, leather, wool, resins, and aniline. It is a strong acid and forms beautifully crystalline salts, which explode violently when heated or struck. It crystallizes from alcohol or water in yellow plates or prisms, melting at  $122^\circ$ , is only sparingly soluble in water, and the aqueous solutions have a persistent deep-yellow colour. It is used for the preparation of explosives, and is also a yellow dye.

**Picryl chloride**,  $\text{C}_6\text{H}_2(\text{NO}_2)_3\text{Cl}$  (from picric acid and  $\text{PCl}_5$ ), resembles the acid chlorides (p. 423) in behaviour. Picric

acid forms beautifully crystallizing additive compounds with some of the more complex aromatic hydrocarbons, and also with amines and phenols, and as these crystallize well and have sharp melting-points they are used for identifying members of these groups.

**Amino-phenols** are obtained by the reduction of nitro-phenols:



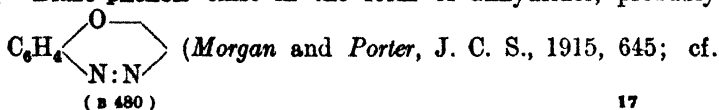
In the amino-phenols (*Hofmann*, 1857) the acid character of the phenols is neutralized by the presence of the amino-group, so that they only yield salts with acids. The amino-phenols themselves are relatively unstable, and readily decompose on exposure to moist air or sunlight, but the hydrochlorides are much more stable. Derivatives of these compounds, as phenols and as amines, are known. The amino-hydrogen is readily replaceable by acyl groups.

*p*-Amino-phenol, m.-pt.  $184^\circ$ , obtained by the electrolysis of nitrobenzene in concentrated sulphuric acid (*Gattermann*), or by molecular rearrangement from  $\beta$ -phenyl-hydroxylamine, or by passing  $p\text{-OH}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2 + \text{H}_2$  over Cu deposited on pumice and heated at  $265^\circ$  (*J. A. C. S.*, 1919, 436), is easily oxidized to quinone,  $\text{C}_6\text{H}_4\text{O}_2$ , and is converted by bleaching-powder into quinone chlor-imide,  $\text{O}:\text{C}_6\text{H}_4:\text{NCl}$ . It is used as a photographic developer under the name of *rodinal*. *Amidol* is a salt of 2 : 4-diamino-phenol, and *metol* is N-methyl-*p*-amino-phenol sulphate and is readily prepared from quinol and methylamine (*J. A. C. S.*, 1919, 270).

*m*-Amino-phenol and diethyl-*m*-amino-phenol,  $\text{C}_6\text{H}_4(\text{OH})[\text{N}(\text{C}_2\text{H}_5)_2]$ , are formed when *m*-amino-benzene-sulphonic acid or its diethyl-derivative is fused with alkali.

The **anisidines**, *amino-anisoles*, *methoxy-anilines*,  $\text{CH}_3\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$ , and the **phenetidines**,  $\text{C}_2\text{H}_5\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$ , are bases similar to aniline, and are used in the colour industry (azo-dyes). **Aceto-*p*-phenetidine**,  $\text{C}_2\text{H}_5\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ , *phenacetine* which forms colourless crystals, is a common anti-pyretic.

**Diazo-phenols** exist in the form of anhydrides, probably



*Bamberger*, B., 1915, 1354). The *m*-compounds do not appear to form such anhydrides (*J. C. S.*, 1917, 497).

**Phenol-sulphonic acids**,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\cdot\text{OH}$ .—The *o*- and *p*-acids are obtained from phenol and concentrated  $\text{H}_2\text{SO}_4$  at a moderate temperature, that is, with much greater ease than the benzene-sulphonic acids; the ortho-acid changes into the para- when its aqueous solution is heated. The two acids may be separated by means of their potassium salts. The *m*-compound can be prepared indirectly by fusing *m*-benzene-disulphonic acid with potash. All three are crystalline.

The *o*- and *m*-acids yield *o*- and *m*-dihydroxy-benzenes when fused with KOH, but the *p*-acid does not react in this way, being attacked only at temperatures over  $320^\circ$ , when complex products are formed. *o*-Phenol-sulphonic acid is used as an antiseptic under the name of "Aseptol" or "*Sozolic acid*"; similarly, the salts of **di-iodo-*p*-phenol-sulphonic acid**,  $\text{OH}\cdot\text{C}_6\text{H}_2\text{I}_2\cdot\text{SO}_3\text{H}$ , "*Sozo-iodol*", form antiseptics resembling iodoform.

## 2. HOMOLOGUES OF PHENOL

The homologues of phenol resemble the latter very closely in most of their properties, form perfectly analogous derivatives, possess disinfecting properties, and also a peculiar odour.

They differ from phenol mainly by the presence of side chains which, as in the case of toluene, &c., may undergo certain transformations. When used in the form of alkyl or acyl derivatives or acid sulphates, they can be oxidized in such a manner that the side chains (methyl groups) are transformed into carboxyl, with the production of hydroxy-carboxylic acids. The cresols themselves cannot be oxidized in this way even by chromic acid mixture, and are completely destroyed by potassium permanganate. Negative substituents, especially if they are present in the *o*-position, render such oxidation more difficult in acid, but facilitate it in alkaline solution.

All three **cresols**,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{OH}$ , are present in coal-tar, and are also contained in the tar from pine and beech wood; they are most readily prepared from the corresponding toluidines.

***m*-Cresol** is conveniently prepared by heating thymol with phosphoric anhydride and then with potash.

***p*-Cresol** is produced during the putrefaction of albumen. Its dinitro-compound is a golden-yellow dye which is used as

ammonium or potassium salt under the name **Victoria orange**. Crude cresol is rendered soluble in water by the addition of resin soap or of oil soap; the preparations so obtained are termed *creoline* and *lysol*, and are employed as antiseptics.

**Thymol**,  $C_{10}H_{14}O$ , 1-methyl-4-isopropyl-3-hydroxy-benzene, an important antiseptic, is found together with cymene,  $C_{10}H_{14}$ , and terpenes,  $C_{10}H_{16}$ , in oil of thyme, *Thymus serpyllum*, and the oil from Ajwan fruit, *Carum copticum*, and on hydrogenation yields menthol (Chap. LVII, B2).

It is used medicinally in hook-worm disease and is a valuable antiseptic. It can be manufactured by the following processes:

1. By the dehydrogenation of piperitone from Australian eucalyptus oil (Chap. LVII, B2) with a Ni or Cu catalyst at  $200^{\circ}$ , but menthone is formed at the same time (B., 1927, 2335).

2. From *p*-cymene (methyl-4-iso-propylbenzene) by the following reactions: nitration in 2 position, reduction to 2-amino, sulphonation to 2-amino-5-sulphonic acid, diazotizing to diazo-cymene-sulphonic acid anhydride, reduction to 1-methyl-4-isopropyl-2-hydrazino-benzene-5-sulphonic acid, removal of  $\cdot NH \cdot NH_2$  group by  $CuSO_4$  and replacement of  $SO_3K$  by OK by fusion with potash (J. A. C. S., 1923, 1489).

3. From 2-nitro-*p*-cymene. Reduction with aluminium amalgam to the 2-NH-OH compound, which with hydrochloric acid gives the 2-amino-5-hydroxy compound, and this diazotized and treated with  $SnCl_2$  and HCl removes the diazo-group yielding thymol (Bull. Soc., 1927, 41, 454).

The isomeric **carvacrol**, 1-methyl-4-isopropyl-2-hydroxy-benzene, present in *Origanum hirtum*, is prepared either by heating camphor with iodine or from its isomer, carvol, and glacial phosphoric acid.

The *constitutions* of these two phenols have been established as follows: (a) Both yield cymene (*p*-methyl-isopropyl-benzene) when heated with phosphorus sulphide and similar compounds. (b) Carvacrol, when heated with phosphorus pentoxide, yields propylene and *o*-cresol. (c) Thymol, when similarly treated, yields propylene and *m*-cresol.



**Eugenol** is the chief constituent of oil of cloves and cinnamon leaf oil and is used for manufacturing vanillin (Chap. XXV, D.).

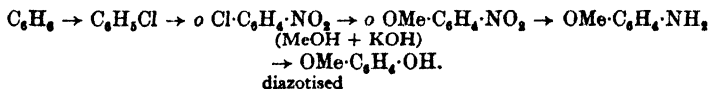
**Safrol**, 1-allyl-3:4-methylenedioxy benzene constitutes 85 per cent of sassafras oil.

## B. Dihydric Phenols

These are analogous to the monohydric compounds in most of their relations, but differ from them in the same way as the dihydric alcohols from the monohydric. The methods of formation are analogous to those used for the monohydric phenols, especially by fusion of sulphonic acids and halogen derivatives with potash; instead, however, of the compound expected, an isomeride which is stable at that high temperature frequently results (see Resorcinol). The *p*-dihydroxy-compounds are characterized by their close connexion with the quinones. Many of the polyhydric phenols are strong reducing agents.

**Catechol**, formerly called **pyrocatechin**,  $C_6H_4(OH)_2$  (1 : 2), which was first obtained by the distillation of catechin (*Mimosa catechu*), is present in raw beet-sugar, and is obtained when many resins or *o*-phenol-sulphonic acid are fused with potash. It crystallizes in short, white, rhombic prisms, which can be sublimed, and dissolves readily in water, alcohol, and ether.

It is usually prepared by heating its mono-methyl ether, **guaiacol**,  $C_6H_4(OH)(OCH_3)$ , a constituent of beech-wood tar, with hydriodic acid (see Anisole, p. 477), or synthetically from benzene by the following series of reactions:



Like most polyhydric phenols, catechol is very unstable in alkaline solution, which quickly becomes green and then black in the air. The aqueous solution is coloured green by ferric chloride, and then violet by ammonia (reactions of the *o*-dihydroxy-compounds). It possesses reducing properties, and precipitates silver even from a cold solution of silver nitrate. By the continued action of chlorine upon it, derivatives of cyclo-pentane and finally of the fatty series result (*Zincke* and *Küster*). By boiling it with potash and potassium methylsulphate, it may be reconverted into guaiacol. Guaiacol, its benzoate and its carbonate,  $OMe\cdot C_6H_4\cdot O\cdot CO\cdot O\cdot C_6H_4\cdot OMe$ , are used medicinally.

**Resorcinol**, or *m*-Dihydroxy-benzene (*Hlasiwetz*, *Barth*, 1864),

is obtained when many resins (Galbanum, Asafoetida), *m*-phenol-sulphonic acid, all three bromo-benzene-sulphonic acids, or *m*- and *p*-benzene-disulphonic acids are fused with potash. The last-mentioned compounds are employed for its preparation on the technical scale. It crystallizes in rhombic prisms or plates, which quickly become brown in the air, dissolves readily in water, alcohol, and ether, and reduces an aqueous solution of silver nitrate when warmed with it, and an alkaline solution even in the cold. With ferric chloride it gives a dark-violet coloration. It acts therapeutically like carbolic acid, only more mildly.

When heated with phthalic anhydride, it is converted into fluorescein (Chap. XXX, 4) (test for *m*-dihydroxy-benzenes), and it is therefore manufactured on the large scale. Nitrous acid or diazonium compounds transform it into azo-dyes (Chap. LIX, B.). Its trinitro-derivative is **styphnic acid**,  $C_6H(OH)_2(NO_2)_3$ , which is formed by the action of nitric acid upon many gum resins.

**Quinol**, formerly called **hydroquinone**, *p*-dihydroxy-benzene (Wöhler, 1844), may be obtained by the oxidation of quinic acid,  $C_7H_{12}O_6$ , by means of  $PbO_2$ , by the hydrolysis of the glucoside arbutin, and from succinylo-succinic ester (Chap. XVII, F.), &c. It is usually prepared by the reduction of quinone with sulphurous acid, and hence the name hydroquinone. It crystallizes in monoclinic plates or hexagonal prisms, of about the same solubility as its isomers, and may be sublimed. Ammonia colours it reddish-brown, while chromic acid, ferric chloride, and other oxidizing agents convert it into quinone or quinhydrone (Chap. XXV, E.). It melts at  $169^\circ$ , and, being a strong reducing agent, it is used as a developer in photography.

Lead acetate solution yields a white precipitate with a solution of catechol, but none with resorcinol, while quinol is only precipitated in presence of ammonia.

**Orcinol**, or *m*-Dihydroxy-toluene, ( $CH_3:OH:OH = 1:3:5$ ), is found in many lichens (*Rocella tinctoria*, *Lecanora*, &c.). It is formed by the elimination of carbon dioxide from orsellinic acid, e.g. upon fusing extract of aloes with potash, and it can also be prepared synthetically from toluene. Of especial interest is its synthesis from ethyl acetone-dicarboxylate (Chap. X, F.) and sodium (Ingold, J. C. S., 1922, 1143). It does not yield a fluorescein with phthalic anhydride.



**Homo-catechol**,  $C_6H_3(CH_3)(OH)_2$ , ( $CH_3:OH:OH = 1:3:4$ ), deserves mention on account of its mono-methyl ether **creosol**,  $CH_3 \cdot C_6H_3(OH)(O \cdot CH_3)$ , occurring in beech-wood tar. Creosol is a liquid similar to guaiacol, boiling at  $220^\circ$ , and, as a derivative of catechol, gives a green coloration with ferric chloride.

**Quinitol** (*Cyclo-hexane-1:4-diol*), *p*-**dihydroxy-hexamethylene**,  $C_6H_{10}(OH)_2$ , a dihydroxy-derivative of reduced benzene, is obtained synthetically by the reduction of *p*-diketo-hexamethylene. It crystallizes in crusts, and has a sweet taste with a bitter after-taste; m.-pt.  $144^\circ$ . It is the simplest representative of the inosite sugar group (this Chap., C.).

### C. Trihydric Phenols

**Pyrogallol**, *Pyrogallie acid* (Scheele, 1786), 1:2:3-**trihydroxy-benzene**, is the most important of these three isomers. It is obtained, apart from synthetical reactions, by heating gallic acid, when carbon dioxide is eliminated:  $C_6H_2(OH)_3 \cdot CO_2H = C_6H_3(OH)_3 + CO_2$ . It crystallizes in white plates, melts at  $132^\circ$ , is readily soluble in water, and capable of subliming without decomposition. It is an energetic reducing agent, e.g. for silver salts, and is used as a developer in photography. Its alkaline solution rapidly absorbs oxygen, hence its use in gas analysis.

In the presence of NaOH the oxidation product appears to be a hexa-hydroxy-triphenoquinone,  $O:C_6H_2(OH)_2:C_6H_2(OH)_2:C_6H_2(OH)_2:O$  (J. C. S., 1915, 1217), or in the presence of  $Ba(OH)_2$  2:3:4:2':3':4'-hexa-hydroxy-diphenyl,  $(OH)_3C_6H_2:C_6H_2(OH)_3$  (A., 1912, 394, 249).

The aqueous solution is coloured bluish-black by a solution of ferrous sulphate containing ferric salt, and purple-red by iodine. It does not react with hydroxylamine (cf. Phloroglucinol).

**Pyrogallol dimethyl ether**,  $C_6H_3(OH)(OCH_3)_2$  (Hofmann), is contained in beech-wood tar, as are also the dimethyl ethers of the compounds  $C_6H_2(CH_3)(OH)_3$  and  $C_6H_2(C_3H_7)(OH)_3$ , homologous with pyrogallol.

**Phloroglucinol**, or 1:3:5-**Trihydroxy-benzene** (Hlasiwetz, 1855), is obtained by the fusion of various resins and of resorcinol with potash or soda, by the action of alkali upon the glucoside phloretin, and by fusing its dicarboxylic ester (whose

synthetical formation is given on p. 510) with potash. It forms large prisms which weather in the air, melts at  $218^{\circ}$ , and sublimes without decomposition. With ferric chloride it gives a dark-violet coloration, its solutions in alkalis readily absorb carbon dioxide, and it possesses reducing properties.

Phloroglucinol is a typical tautomeric compound.

In many reactions, e.g. (a) the formation of metallic derivatives,  $C_6H_3(OK)_3$ ; of a trimethyl ether,  $C_6H_3(OCH_3)_3$ , which is insoluble in alkali; and of a triacetyl derivative,  $C_6H_3(OAc)_3$ ; (b) its combination with phenyl-carbimide to form a tricarbani-line derivative,  $C_6H_3(O \cdot CO \cdot NH \cdot C_6H_5)_3$ , it reacts as a normal phenol, i.e. as sym. trihydroxy-benzene. On the other hand, however, in certain of its reactions it behaves as a ketone, i.e.

as triketo-hexamethylene,  $CO \begin{array}{c} \diagup CH_2 \cdot CO \diagdown \\ \diagdown CH_2 \cdot CO \diagup \end{array} CH_2$ ; thus it yields

a trioxime,  $C_6H_6(:N \cdot OH)_3$ , and when alkylated in presence of alcoholic potash yields tetra- and hexa-alkyl derivatives, e.g.

$C_6Me_6O_3$ ,  $CO \begin{array}{c} \diagup CMe_2 \cdot CO \diagdown \\ \diagdown CMe_2 \cdot CO \diagup \end{array} CMe_2$ . Its ultra-violet absorption

spectrum (Hedley, J. C. S., 1906, 730) resembles that of other phenols.

**Hydroxy-quinol**, 1 : 2 : 4-Trihydroxy-benzene, is obtained by fusing quinol with potash. Like pyrogallol, it yields no oxime with hydroxylamine.

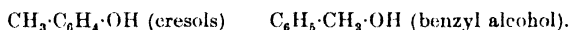
**Hexahydroxy-benzene**,  $C_6(OH)_6$ , forms as its potassium salt potassium carboxide,  $C_6O_6K_6$ , the explosive compound sometimes obtained in the manufacture of metallic potassium. It crystallizes in colourless prisms, has no definite melting-point, but decomposes at about  $200^{\circ}$ , and can be converted into its quinone.

**Quercitol**,  $C_6H_7(OH)_5$ , found in the oak, and **inosite** or **inositol**,  $C_6H_8(OH)_6$ , found in the muscles of the heart, are polyhydroxy-derivatives of cyclo-hexane. In many respects they closely resemble the aliphatic polyhydric alcohols rhamnitol and sorbitol. Quercitol melts at  $235^{\circ}$ , is optically active, and has  $[\alpha]_D = +24.16$ . Inositol or hexahydroxy-cyclo-hexane exists in five inactive and in *d*-, *l*-, and *r*-modifications.

## XXV. AROMATIC ALCOHOLS, ALDEHYDES, AND KETONES

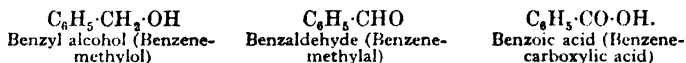
## A. Aromatic Alcohols

Isomeric with certain phenols are the aromatic alcohols which closely resemble the aliphatic hydroxy compounds. The simplest and most important of these is benzyl alcohol,  $C_7H_7\cdot OH$ , which is isomeric with the cresols.



Characteristic of all aromatic alcohols is the fact that the hydroxyl group is attached to a carbon atom of a side chain and not to a carbon atom of the nucleus. It is thus clear that each alcohol will have one or more phenols isomeric with it. The three cresols, *o*-, *m*-, *p*-methylphenols are isomeric with benzyl alcohol and  $\beta$ -phenylethyl alcohol is isomeric with the dimethylphenols and with the ethylphenols. The alcohols are also isomeric with the phenolic ethers, e.g. benzyl alcohol with phenyl methyl ether.

The formula,  $C_6H_5\cdot CH_2\cdot OH$ , for benzyl alcohol follows from the formation of the alcohol from benzyl chloride,  $C_6H_5\cdot CH_2Cl$  (and vice versa), and also from the fact that it can be oxidized to an aldehyde and an acid containing the same number of carbon atoms in the molecule as itself:



Benzyl alcohol may also be looked upon as methyl alcohol in which one atom of hydrogen is replaced by the group  $C_6H_5$ :



and is therefore the simplest aromatic alcohol.

As in the fatty series, so in the aromatic, the alcohols can be classified into the three main groups: primary, secondary, and tertiary. The primary contain the group  $-CH_2\cdot OH$ , the secondary the group  $=CH\cdot OH$ , and the tertiary the group  $\equiv C\cdot OH$ , and all must have at least one aryl group attached to the characteristic group. In triphenylcarbinol,  $(C_6H_5)_3C\cdot OH$ , all three alkyl groups are aromatic, but this is not essential,

e.g. phenyldimethylcarbinol,  $\text{C}_6\text{H}_5\cdot\text{C}(\text{CH}_3)_2\cdot\text{OH}$  is a tertiary aromatic alcohol.

The primary, secondary, and tertiary are differentiated in exactly the same manner as the corresponding groups in the aliphatic series. Thus the primary yield on oxidation first aldehydes and then acids containing the same number of carbon atoms, the secondary yield ketones, e.g.  $(\text{C}_6\text{H}_5)_2\text{CH}\cdot\text{OH}$  yields  $(\text{C}_6\text{H}_5)_2\text{CO}$ , benzophenone, and the tertiary are not readily oxidized.

Of the polyhydric alcohols, phenyl-glycerol (1-phenyl-1:2:3-trihydroxypropane) is the most important. All of these contain the hydroxyl radicals attached to carbon atoms of the side chain and not to those of the nucleus, and this is the fundamental difference between an aromatic alcohol and a phenol. The alcohols are not of the same commercial importance as the phenols, and hence have not been investigated to the same extent.

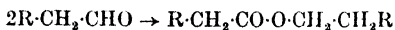
Only a few occur naturally, e.g.  $\beta$ -phenylethyl alcohol; they are usually prepared by laboratory methods, e.g. the primary by the reduction of the esters of aromatic acids by *Bouveault's* method, or of the acid amides; the secondary by the reduction of ketones or by the aid of *Grignard's* reagents and aldehydes, and the tertiary by the same method from esters or ketones (Chap. IV, H.).

These alcohols closely resemble the alcohols of the fatty series, so far as regards the formation of alcoholates, ethers, esters, mercaptans, amines, phosphines, &c. They are, however, at the same time benzene derivatives, and consequently yield chloro-, bromo-, nitro-, amino-, &c., substitution products. Unsaturated aromatic alcohols are also known, which resemble the unsaturated aliphatic compounds in their chemical behaviour, but are at the same time benzene derivatives.

**Benzyl alcohol**,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{OH}$ , is a colourless liquid of faint aromatic odour, sparingly soluble in water, and boils at  $204^\circ$ . It occurs naturally in Peru and Tolu balsams as benzoic and cinnamic esters, and is formed from benzyl chloride just as alcohol is from ethyl chloride. It is usually prepared by the action of concentrated aqueous potash on benzaldehyde, whereby the one half of the aldehyde is oxidized and the remainder reduced (B., 1881, 2394; *Cannizzaro* reaction, 1853, a process often termed dismutation):



This type of reaction occurs with most substituted benzaldehydes with the exception of those containing OH groups, and also occurs with aliphatic aldehydes which do not readily polymerize to aldols (Chap. IX, C.), and by using aluminium or magnesium alkoxides it is possible to obtain the ester formed by the reaction of the acid with the alcohol, e.g.:



(*Child and Atkins*, J. A. C. S., 1923, 3013; 1925, 798).

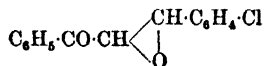
Benzyl alcohol is also formed when benzamide is reduced with sodium amalgam. This is a reaction which has been employed for the preparation of a number of substituted benzyl alcohols (*Hutchinson*, B., 1891, 173).

**Phenyl-ethyl alcohol**,  $C_6H_5\cdot CH_2\cdot CH_2\cdot OH$ , b.-pt.  $220^\circ$ , is prepared by reducing ethyl phenylacetate with sodium and alcohol, *Bouveault* and *Blanc's* method (Chap. XLVII, A.). It is an important constituent of rose oil and of many blended perfumes.

**Phenyl-methyl-carbinol**,  $C_6H_5\cdot CH(OH)\cdot CH_3$ , b.-pt.  $203^\circ$ , can be prepared by reducing acetophenone,  $C_6H_5\cdot CO\cdot CH_3$  (this Chap., C.) into which it is reconverted by gentle oxidation.

The simplest of the unsaturated alcohols is **cinnamic alcohol**,  $C_6H_5\cdot CH:CH\cdot CH_2OH$ , which occurs as cinnamic ester ("styracin") in storax. It crystallizes in glistening needles of hyacinth-like odour, yields cinnamic acid when gently oxidized, and benzoic when the oxidation is more vigorous.

Ethylene oxides containing aryl substituents are much more stable than those containing aliphyl-groups (p. 218, A.). Thus *w*-bromoacetophenone,  $C_6H_5\cdot CO\cdot CH_2Br$ , readily condenses in the presence of NaOEt with substituted benzaldehydes containing negative groups, yielding **ethylene oxides** of the type,



(cf. B., 1917, 1457, and 1918, 192).

## B. Aromatic Aldehydes

**Benzaldehyde**, *Benzene-methylal*, or *oil of bitter almonds*,  $C_6H_5\cdot CHO$ , discovered in 1803 and investigated by *Liebig*

and *Wöhler*, is a colourless, strongly refracting liquid of agreeable bitter almond-oil odour. It boils at  $179^{\circ}$ , has a sp. gr. 1.05 at  $15^{\circ}$ , and is readily soluble in alcohol and ether, but only sparingly in water (1 in 30).

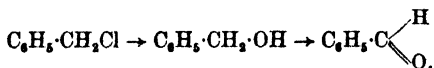
Many of the modes of formation are analogous to those described under the aliphatic aldehydes (Chap. V, A.):

(a) By the oxidation of the corresponding alcohol. This reaction is of little practical value, as the alcohols themselves are usually prepared from the aldehydes.

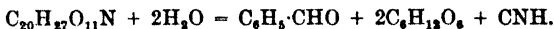
(b) By the distillation of the calcium salt of the corresponding acid, benzoic acid, with calcium formate.

(c) By heating the corresponding dichloride, benzal chloride, or benzylidene chloride,  $C_6H_5 \cdot CHCl_2$  (from toluene), with water or sulphuric acid, or, as is done on the technical scale, with water and lime; also by heating benzyl chloride,  $C_6H_5 \cdot CH_2Cl$ , with water and plumbous or cupric nitrate, or the bromide with sodium nitrate (U. S. P.), or by oxidizing the chloride with sodium dichromate and caustic soda (E. P.).

This method involves processes of hydrolysis and oxidation:



(d) Together with dextrose and hydrocyanic acid by decomposing **amygdalin**,  $C_{20}H_{27}O_{11}N$ , a glucoside (see Glycosides, Chap. LVI, F.) which occurs in bitter almonds and crystallizes in white plates, either by means of sulphuric acid or by emulsin (an enzyme likewise present in bitter almonds) (Chap. LXIX, D.):

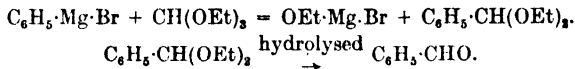


(e) By the action of chromyl chloride,  $CrO_2Cl_2$ , upon toluene. This is *Etard's* reaction (1881), and is of great value for the synthesis of aldehydes and also of certain ketones from hydrocarbons. An additive compound,  $C_6H_5 \cdot CH_3(CrO_2Cl_2)_2$ , is first formed, and yields the aldehyde on the addition of water (B., 1884, 1462, 1700; 1899, 1050; J. C. S., 1907, 259).

$MnO_2$  and dilute  $H_2SO_4$  can also be used as oxidizing agents, or even better  $CrO_3$  with acetic anhydride when the diacetate,  $R \cdot CH(OAc)_2$ , is formed, and prevents further oxidation (A., 1900, 311, 353).

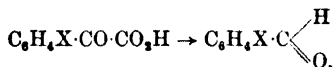
(f) By the action of *Grignard's* phenyl-magnesium bromide on

ethyl orthoformate (*Bodroux*, C. R., 1904, **138**, 92 and 700), e.g.:



*Gattermann* and *Maffezzoli* (B., 1903, 4152) have used *Grignard's* compound with a large excess of ethyl formate at low temperatures.

(g) Homologues of benzaldehyde are sometimes prepared by the elimination of carbon dioxide from substituted phenylglyoxylic acids by a process of distillation:

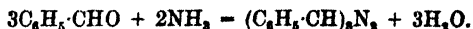


(h) A simple synthesis can be effected by heating the hydrocarbon with carbon monoxide under a pressure of 50–90 atmospheres (E. P., 1915; cf. J. I. E. C., 1933, 497), or by action of a mixture of CO and HCl (reacting as H·CO·Cl) on the hydrocarbon with a little CuCl (*Gattermann*, A., 1906, **347**, 347).

(i) By passing hydrogen into a boiling 20 per cent solution of benzoyl chloride in xylene, using palladinized BaSO<sub>4</sub> as catalyst (cf. Chap. VII, B).

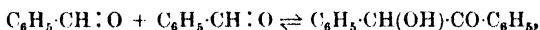
*Behaviour*.—1. Its behaviour is that of an aldehyde, and in many respects it closely resembles the aliphatic aldehydes. Thus it is (a) easily oxidizable to the acid, and on this account reduces an ammoniacal silver solution with the production of a mirror; (b) reducible to the alcohol; (c) capable of forming a crystalline additive compound with NaHSO<sub>3</sub>; (d) capable of combining with HCN (see Mandelic Acid); (e) capable of reacting with hydroxylamine and phenylhydrazine to benzaldoxime, C<sub>6</sub>H<sub>5</sub>·CH:N·OH, and benzaldehyde-phenylhydrazine, C<sub>6</sub>H<sub>5</sub>·CH:N<sub>2</sub>H·C<sub>6</sub>H<sub>5</sub>, respectively; (f) converted into benzylidene chloride, C<sub>6</sub>H<sub>5</sub>·CHCl<sub>2</sub>, by the action of PCl<sub>5</sub>.

2. Benzaldehyde does not form an additive compound with ammonia analogous to the aldehyde ammonias of the aliphatic series, but enters into a somewhat complex condensation, yielding hydrobenzamide:



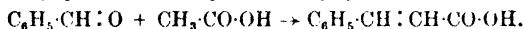
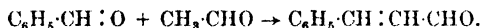
3. Benzaldehyde and its homologues can undergo polymerization, e.g. when an alcoholic solution of benzaldehyde is

boiled with potassium cyanide, **benzoin** is formed (a balanced reaction, J. A. C. S., 1923, 836):



a compound which is both a secondary alcohol and a ketone.

4. *Condensations*: (a) The O atom of the  $\cdot\text{CHO}$  group is remarkably reactive, and usually reacts with the  $\text{H}_2$  of a methylene group provided this is attached to CO, CN,  $\text{NO}_2$ , a benzene nucleus or a conjugated system, and this type of *condensation* serves for the preparation of hydroxyaldehydes, unsaturated ketones, unsaturated acids, unsaturated nitro-compounds, and unsaturated nitriles, e.g.:



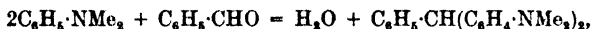
In most cases a condensing agent is required.

(b) With aromatic arylamines they form benzyldiene derivatives, **azomethines** or **Schiff's bases**:



An intermediate product is the additive compound  $\text{R}\cdot\text{CH}(\text{OH})\cdot\text{NHR}$ , which loses water yielding the azomethine. A few such additive compounds have actually been isolated (*Dimroth and Zoepritz*, B., 1902, 984; 1906, 2810; *Lowy* and others, J. A. C. S., 1921, 344, 626).

(c) With tertiary amines, e.g.:



when a substituted diamino-derivative of triphenyl-methane is produced (Chap. XXX, 1).

5. The dismutation under the influence of alkalis (*Cannizzaro* reaction) with the formation of alcohol and acid has already been referred to (Chap. XXV, A.).

6. As a benzene derivative, it can be substituted by halogens (indirectly), and can be nitrated, sulphonated, &c. (directly).

At the boiling temperature chlorine enters the side chain, yielding benzoyl chloride,  $\text{C}_6\text{H}_5\cdot\text{COCl}$  (cf. Toluene).

Among its derivatives the following deserve mention:

$\alpha$ -**Benzaldoxime**, *Benz- $\alpha$ -aldoxime*,  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{N}\cdot\text{OH}$ , melts at  $35^\circ$ , and decomposes when boiled. It can be transformed by means of acids into the isomeric  $\beta$ -**benzaldoxime**, which



melts at  $125^{\circ}$  (for velocity cf. *Patterson*, J. C. S., 1907, 504; 1908, 1041), and in contradistinction to the isomer, readily reacts with acetic anhydride yielding benzonitrile. The oximes are stereo-isomeric (Chap. L, C1).

**Benzaldehyde - phenyl - hydrazone**,  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{N}\cdot\text{NHC}_6\text{H}_5$ , forms colourless crystals, melting at  $152^{\circ}$ . **Benzylideneazine**,  $\text{CHPh}:\text{N}:\text{N}:\text{CHPh}$ , from benzaldehyde and hydrazine sulphate, has m.-pt.  $93^{\circ}$ .

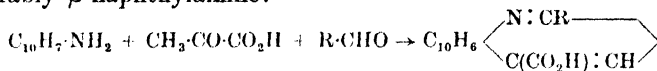
**Nitro-benzaldehydes**,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CHO}$ .-- The *m*-compound is the chief product of nitration, but some 20 per cent of the *o*-compound is formed at the same time. The latter is prepared by oxidizing *o*-nitro-cinnamic acid by  $\text{KMnO}_4$ , in presence of benzene; it forms long colourless needles, melting at  $46^{\circ}$ , yields indigo (Chap. XLI, C.) with acetone and caustic soda, and on exposure to sunlight forms *o*-nitroso-benzoic acid. It can be reduced to *o*-amino-benzaldehyde,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CHO}$ , a compound crystallizing in silvery glistening plates, m.-pt.  $46^{\circ}$ , which is of value for various synthetical reactions (see Quinoline, Chap. XLIV, A2). *m*-Amino-benzaldehyde, prepared by reducing the bisulphite compound of *m*-nitro-benzaldehyde, is used in the production of triphenyl-methane dyes (Chap. XXX).

**Cinnamaldehyde**,  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{CHO}$ , is the chief constituent of oil of cinnamon (*Cinnamomum zeylanicum*) of Ceylon, and oil of cassia (*C. cassia*) of China, from which it may be isolated by means of its bisulphite-compound. It is an oil of aromatic odour, boils at  $246^{\circ}$ , and is readily volatile with steam. In addition to its properties as an aldehyde, it also possesses the properties of an unsaturated compound, e.g. forms a dibromide. Its reaction with potassium hydrogen sulphite is characteristic. It first forms an additive compound,  $\text{C}_6\text{H}_5\text{CH}:\text{CH}\cdot\text{CH}(\text{OH})(\text{SO}_3\text{K})$ , like an ordinary aldehyde, and then, as an unsaturated compound, combines with a second molecule of the sulphite; yielding  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{SO}_3\text{K})\cdot\text{CH}_2\cdot\text{CH}(\text{OH})(\text{SO}_3\text{K}) + 2\text{H}_2\text{O}$ . (B., 1891, 1805; 1898, 3301.)

When cinnamaldehyde is used in many of the condensations mentioned on p. 493 the product contains two olefine linkings, thus with malonic ester the product,  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}:\text{CH}:\text{C}(\text{CO}_2\text{Et})_2$ , ethyl cinnamylidene-malonate is formed.

Particular aldehydes are usually identified by the melting-points of their *p*-nitrophenyl- or 2:4-dinitrophenyl-hydrazones or by *Doebner* reaction (B., 1894, 352), where the aldehyde is

condensed with pyruvic acid and a primary arylamine, preferably  $\beta$ -naphthylamine:



The acid readily loses  $\text{CO}_2$  and an  $\alpha$ -aryl- $\beta$ -naphthoquinoline of definite melting-point is formed.

### C. Aromatic Ketones

The aromatic ketones are usually divided into (1) mixed ketones, aryl-alkyl ketones, e.g.  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3$ , and (2) true aromatic or diaryl ketones, e.g.  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{C}_6\text{H}_5$ .

**Acetophenone**, *Phenyl methyl ketone*,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3$ , crystallizes in colourless plates, is readily soluble in water, melts at  $20^\circ$ , boils at  $200^\circ$ . It is obtained by the normal modes of preparation for ketones, e.g. by distilling a mixture of acetate and benzoate of calcium, as also by the *Friedel-Crafts* synthesis (p. 405), viz. the conjoint action of acetyl chloride and aluminium chloride upon benzene. Sulphoacetic acid (acetic anhydride and sulphuric acid) can be substituted for the acid chloride and  $\text{AlCl}_3$ , e.g. in the case of guaiacol (B., 1922, 1892; J. pr., 1921 [ii], 103, 329). When benzene and its derivatives are converted into ketones by this method, only one acyl group is introduced as a rule, and this into the para-position with respect to any alkyl group already present. With a sym. trialkylated benzene, e.g. mesitylene, it has been found possible to introduce two acyl groups, e.g. diacetyl-mesitylene,  $(\text{CH}_3)_3\text{C}_6\text{H}(\text{COCH}_3)_2$  (V. Meyer, B., 1895, 3212; 1896, 846, 1413). When the temperature is kept low by diluting the mixture with carbon disulphide, a good yield of ketone may be obtained by the *Friedel-Crafts* method.

Acetophenone unites in itself the properties of a ketone of the fatty series and of a benzene derivative. It yields benzoic acid and carbon dioxide when oxidized with ordinary oxidizing agents, but with cold alkaline permanganate it yields  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CO}_2\text{H}$ , **phenyl-glyoxylic acid** or **benzoyl-formic acid**. When warmed with halogens, it is substituted in the side chain (e.g. to "**phenacyl bromide**",  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\text{Br}$ ), and with nitric acid it is nitrated. It is used as a soporific under the name of "*Hypnone*". Its **oxime** melts at  $59^\circ$ , and its

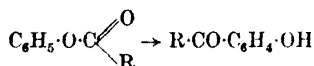
**phenyl-hydrazone** at  $105^{\circ}$ . It combines with hydrogen cyanide to form the nitrile of  $\alpha$ -phenyl-lactic acid, but cannot form an additive compound with sodium hydrogen sulphite.

Its homologues closely resemble it, but are liquid at the ordinary temperature. Acetophenone and some of its homologues can be prepared from hydrocarbons with long side chains by *Etard's* reaction (see p. 491: B., 1890, 1070; 1891, 1356). Aromatic polyketones (cf. p. 254) have also been prepared, e.g. **benzoyl-acetone**,  $C_6H_5 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$ , and **acetophenone-acetone**,  $C_6H_5 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO \cdot CH_3$ . The latter, like acetonyl-acetone, is readily converted into furane, pyrrole, and thiophene derivatives (Chap. XL).

Benzaldehyde condenses with acetone and acetophenone in the presence of alkalis, yielding unsaturated ketones, e.g. **Benzylideneacetone**,  $CHPh:CH \cdot CO \cdot CH_3$ , m.-pt.  $41^{\circ}$ , and **benzylidene-acetophenone**, *chalcone*,  $CHPh:CH \cdot CO \cdot C_6H_5$ , m.-pt.  $58^{\circ}$ .

**Benzophenone**, *Diphenyl-ketone*,  $C_6H_5 \cdot CO \cdot C_6H_5$ , may be obtained (1) by distilling calcium benzoate, (2) by the *Friedel-Crafts* synthesis, (3) by the oxidation of diphenylmethane,  $(C_6H_5)_2CH_2$ , or of diphenyl-carbinol,  $(C_6H_5)_2CH \cdot OH$ .

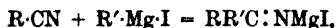
Ketones are also formed by the wandering of acyl groups from phenolic esters, e.g.:



(cf. Abs., 1928, A., 1011, 1013).

Good yields of ketones are not usually obtained by the action of *Grignard's* reagents on acid chlorides; as a rule the reaction proceeds farther, and a tertiary alcohol is obtained (Chap. IV, H.). An exception is found in the reaction between  $\alpha$ -naphthyl-magnesium bromide and benzoyl chloride.

Ketones can (*Blaise*, C. R., 1901, 132, 38; 133, 299) be synthesized from *Grignard's* reagents and nitriles, or amides:



and this with water gives  $R \cdot CO \cdot R' + NH_3 + I \cdot Mg \cdot OH$ . Acid amides react in a somewhat similar manner.

Benzophenone is dimorphous; the stable modification melts at  $49^{\circ}$ , and when boiled or distilled yields the unstable modification, melting at  $26^{\circ}$ ; but this gradually passes back again

into the stable modification. The reaction is, however, considerably accelerated by the addition of a minute crystal of the stable compound. It yields an **oxime** melting at  $140^{\circ}$  and a **phenyl-hydrazone** melting at  $105^{\circ}$ .

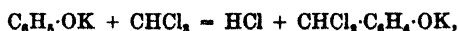
When reduced with zinc dust or hydriodic acid and red phosphorus, it yields diphenylmethane.

## D. Hydroxy or Phenolic Alcohols, Aldehydes, and Ketones

Formula	Name	Constitution
$\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{OH}$ .. ..	Saligenin, <i>o</i> -hydroxy-benzyl-alcohol.	
$\text{OCH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{OH}$ .. ..	Anisyl alcohol, <i>p</i> -methoxy-benzyl alcohol.	
$\text{OH}\cdot\text{C}_6\text{H}_3(\text{OMe})\cdot\text{CH}_2\text{OH}$ .. ..	Vanil alcohol, 3-methoxy-4-hydroxy-benzyl alcohol.	
$\text{OH}\cdot\text{C}_6\text{H}_3(\text{OMe})\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{OH}$	Coniferyl alcohol, $[\text{OCH}_3:\text{OH} = 3:4]$ .	
$\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CHO}$ .. ..	Salicyl-aldehyde, <i>o</i> -hydroxy-benzaldehyde.	
$\text{OCH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CHO}$ .. ..	Anisaldehyde, <i>p</i> -methoxy-benzaldehyde.	
$(\text{OH})_2\text{C}_6\text{H}_3\cdot\text{CHO}$ .. ..	Procatechuic aldehyde, 3:4-dihydroxy benzaldehyde.	
$\text{OH}\cdot\text{C}_6\text{H}_3(\text{OMe})\cdot\text{CHO}$ .. ..	Vanillin, 3-methoxy-4-hydroxy-benzaldehyde.	
$\text{CH}_3\text{O}_2:\text{C}_6\text{H}_3\cdot\text{CHO}$ .. ..	Piperonal, methylene-procatechuic aldehyde.	

A large number of compounds are known which possess phenolic properties in addition to those of an alcohol, aldehyde, or ketone. Several of these compounds occur as glucosides in nature. Anisaldehyde is obtained from the oxidation of anisole (methyl phenyl ether).

*Tiemann-Reimer's* synthesis consists in heating a phenol with chloroform in the presence of concentrated KOH:

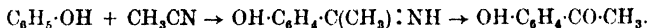


and the dichlor-derivative thus formed is hydrolysed by the alkali to  $\text{CHO}\cdot\text{C}_6\text{H}_4\cdot\text{OK}$ . The formyl-group  $\cdot\text{CH}:\text{O}$  always takes up the *o*- or *p*-position with respect to the hydroxy-group, and, as a rule, the *o*- and *p*-compounds are formed

together, and may often be separated by the difference in volatility of the two compounds in steam.

In the *Gattermann* synthesis (B., 1915, 1112), a phenol is heated with HCN and HCl, reacting as  $\text{Cl}-\text{C} \begin{array}{l} \nearrow \text{H} \\ \searrow \text{NH} \end{array}$ , and sub-

sequent hydrolysis of the compound  $\text{R}\cdot\text{CH}:\text{NH}$ . If an alkyl cyanide is used, hydroxy-ketones are the final products:



An analogous synthesis is passing a rapid current of dry HCl into an ethereal solution of cyanogen bromide and resorcinol or some other polyhydric phenol (*Karrer*, *Helv.*, 1919, 89).

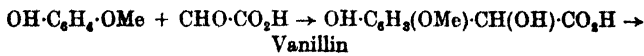
**Vanillin** crystallizes in beautiful needles, and is prepared on the large scale from **coniferin**,  $\text{C}_{16}\text{H}_{22}\text{O}_8 + 2\text{H}_2\text{O}$ , a compound occurring in the sap of the cambium in the *Coniferæ*. This is hydrolysed by acids into glucose and **coniferyl alcohol**,  $\text{C}_6\text{H}_3(\text{OH})(\text{OCH}_3)(\text{C}_3\text{H}_4\cdot\text{OH})$ , and the latter yields vanillin when oxidized (*Tiemann* and *Haarmann*, 1874). The  $\text{CH}_3$  group is removed by heating with hydrochloric acid at  $200^\circ$ , with the formation of *protocatechuic aldehyde*. Vanillin is also found in vanilla pod, asparagus, beet-sugar, asafoetida, and certain balsams. It is a very valuable flavouring matter.

Vanillin can also be obtained synthetically from *m*-chloro-*p*-nitro-benzaldehyde (from *m*-chloro-*p*-nitro-toluene), but is usually manufactured from eugenol (p. 473) which is transformed into isoeugenol,  $\text{OH}\cdot\text{C}_6\text{H}_3(\text{OMe})\text{CH}:\text{CH}\cdot\text{CH}_3$  by alcoholic potash, then acetylated and finally oxidized with chromic acid.

It is also manufactured by the following processes:

(1) Guaiacol with chloral hydrate and alkali yields guaiacol trichloro-methylcarbinol  $\text{OH}\cdot\text{C}_6\text{H}_3(\text{OMe})\cdot\text{CH}(\text{OH})\cdot\text{CCl}_3$ , which on hydrolysis and oxidation with a copper salt gives vanillin (1923).

(2) Glyoxylic acid obtained by electrolytic reduction of oxalic acid is condensed with guaiacol in dilute alkaline solution and the product oxidized (1932):



The corresponding ethyl ether  $\text{OH}\cdot\text{C}_6\text{H}_3(\text{OEt})\cdot\text{CHO}$  called **ethyl vanillin** is prepared from **safrol** (p. 483).

## E. Quinones

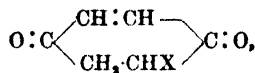
Quinones are compounds derived from benzene and its derivatives by the replacement of two atoms of hydrogen by two of oxygen, e.g.  $C_6H_4O_2$ . As a group they are characterized by (a) their yellow colour, (b) being readily reduced to dihydric phenols, and hence often acting as oxidizing agents. They are often divided into **para-quinones** and **ortho-quinones**.

**p-Benzoquinone** or **Quinone**,  $C_6H_4O_2$  (1838), formed by oxidizing quinol with chromic acid, crystallizes in yellow needles or prisms with a pungent odour, is sparingly soluble in water but readily in alcohol and ether, and can be sublimed; m.-pt.  $116^\circ$ . Its homologues, which are numerous, are yellow solids volatile with steam, obtained by oxidizing dihydric phenols, or polyhydric phenols, which contain two hydroxyls in the para-position.

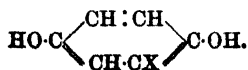
Quinone is also formed by the oxidation of many aniline and phenol derivatives belonging to the para-series, e.g. *p*-amino-phenol, sulphanilic acid, and *p*-phenol-sulphonic acid; it is usually prepared by the oxidation of aniline itself by means of chromic acid (see B., 1887, 2283), but was first obtained by distilling quinic acid with manganese dioxide and sulphuric acid. Exposure to light causes it to turn brown, and it colours the skin yellow-brown. It is readily reduced to quinol by  $SO_2$ , HI,  $SnCl_2$  and HCl, &c., and can therefore act as an oxidizing agent.

In chloroform solution it takes up two or four atoms of bromine to form a di- or tetra-bromide ( $C_6H_4O_2 \cdot Br_4$ ). Under other conditions chlorine and bromine act upon it as substituents.

Many 2- or 2:5-substituted quinols can be obtained by the action of HCl, HBr, H·OR, R·NH<sub>2</sub>, R·SO<sub>2</sub>H, &c., on quinone. An additive product,



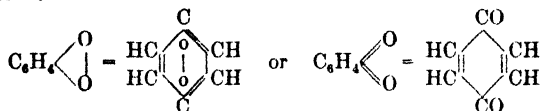
is first formed which is transformed into



It yields sparingly soluble, coloured crystalline compounds with complex hydrocarbons, phenols, phenolic ethers, and amines (*Pfeiffer* \*). With quinol it forms an additive compound termed **quinhydrone**,  $C_6H_4O_2 + C_6H_4(OH)_2$ ; this crystallizes in green prisms with a metallic lustre, and is also formed as an intermediate product in the oxidation of quinol or in the reduction of quinone.

It also forms additive compounds with conjugated dienes (*Diels-Alder Condensation*, Chap. LI, C3).

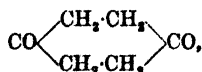
**Constitution.**—Quinone is derived from benzene by the exchange of two atoms of hydrogen for two of oxygen, which, from the close connexion between quinone and quinol, must be in the *p*-position. The constitution of quinone may be explained either by assuming that these two oxygen atoms are linked together, so that the benzene nucleus remains unchanged, or that the latter experiences a partial reduction, with the formation of a derivative of  $C_6H_8$ , a "diketo-dihydrobenzene":



According to the first of these two formulæ, quinone would be a peroxide: according to the second, a ketone. In favour of the latter view (which was brought forward by *Fittig*, and is now almost universally accepted) are (1) the fact that quinone yields an oxime,  $C_2H_2 \begin{array}{c} C(N\cdot OH) \\ \diagdown \quad \diagup \\ \quad CO \end{array} C_2H_2$  (identical with nitroso-phenol, Chap. XXIV, A1), and a dioxime, **quinone-**

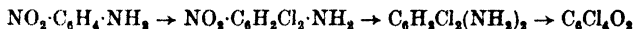
**dioxime**,  $C_2H_2 \begin{array}{c} C(N\cdot OH) \\ \diagdown \quad \diagup \\ C(N\cdot OH) \end{array} C_2H_2$  (B., 1887, 613), and also phenyl-hydrazones; (2) its power of forming additive compounds with bromine; and (3) its relations to the analogously constituted anthraquinone.

**Tetrahydro-quinone**, *p*-Diketo-hexamethylene (*cyclo-hexane-1:4-dione*),



can be prepared by hydrolysing and eliminating the carboxyl groups from succinylsuccinic ester (Chap. XVII, F.). It crystallizes in colourless prisms, melts at  $78^{\circ}$ , and, on reduction, yields quinitol (Chap. XXIV, B.).

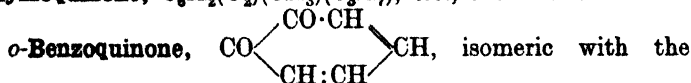
**Chloranil**, *Tetrachloro-quinone*,  $C_6Cl_4O_2$ , which crystallizes in lustrous yellow plates, is obtained by chlorinating quinone and also by oxidizing many organic compounds, e.g. phenol, with HCl and  $KClO_3$ . A good yield may be obtained by chlorinating *p*-nitraniline, reducing the 2 : 6-dichloro-4-nitraniline thus obtained to 2 : 6-dichloro-*p*-phenylene-diamine, and then oxidizing and chlorinating by means of potassium chlorate and hydrochloric acid:



(Witt, Abstr., 1904, 1, 174). When reduced, it yields the colourless tetrachloro-quinol; it also acts as an oxidizing agent, converting, e.g., dimethylaniline into methyl-violet. A dilute solution of potassium hydroxide transforms it into **potassium chloranilate**,  $C_6Cl_2O_2(OK)_2 + H_2O$  (dark-red needles), corresponding with which there is also an analogous nitro-compound, **potassium nitranilate**,  $C_6(NO_2)_2O_2(OK)_2$ . The latter salt is distinguished by its sparing solubility, hence its formation may be made use of as a test for potassium compounds. (For its constitution see B., 1886, 2398.)

Chlorine transforms chloranil and chloranilic acid into complex chloro-products of the hexa- and pentamethylene series, and finally into chlorinated fatty compounds. (For a tabular summary see *Hantzsch*, B., 1889, 2841; cf. also B., 1892, 827, 842.)

**Toluquinone**,  $C_6H_3(O_2)(CH_3)$ , **xyloquinone**,  $C_6H_2(O_2)(CH_3)_2$ , **thymoquinone**,  $C_6H_2(O_2)(CH_3)(C_2H_5)$ , &c., are known.



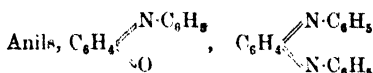
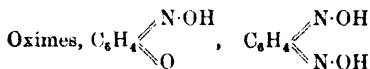
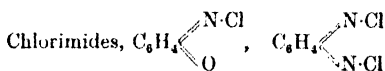
*p*-compound, has been prepared by *Willstätter* and *Pfannenstiel* (B., 1904, 4744) by the oxidation of an ethereal solution of catechol (*o*-dihydroxy-benzene) with silver oxide. It forms pale-red transparent plates, is relatively unstable, and begins to decompose at  $60^{\circ}$ – $70^{\circ}$ . It is readily reduced by sulphur dioxide to catechol, and dyes the skin brown. For two isomeric forms cf. B., 1908, 2580; 1911, 2632



Simple *m*-quinones are not known, but the binolecular **tribromoresoquinone**,  $\text{CO} \begin{array}{c} \diagup \text{CBr:CH} \\ \diagdown \text{CBr}_2\cdot\text{CO} \end{array} \text{C} \begin{array}{c} \diagup \text{CH:CBr} \\ \diagdown \text{CO}\cdot\text{CBr}_2 \end{array} \text{CO}$ , has been prepared (B., 1909, 797, 2814).

## F. Quinone Chlorimides, Quinoneanils, and Anilino-quinones

Characteristic N-derivatives of quinones are:



The *p*-quinone chlorimides are obtained by the oxidation of the *p*-amino-phenols or *p*-phenylene-diamines with bleaching powder, e.g. **quinone chlorimide**,  $\text{O}:\text{C}_6\text{H}_4:\text{NCl}$ , from *p*-amino-phenol hydrochloride, and **quinone dichlorimide**,  $\text{Cl}\cdot\text{N}:\text{C}_6\text{H}_4:\text{N}\cdot\text{Cl}$ , from *p*-phenylene-diamine hydrochloride. The first-named crystallizes in golden-yellow crystals, which are volatile with steam; when reduced it yields amino-phenol, and when boiled with water quinone; the dichlorimide reacts similarly.

**Quinonediiimide**,  $\text{NH}:\text{C}_6\text{H}_4:\text{NH}$ , forms bright yellow, explosive crystals, and on reduction gives *p*-phenylene-diamine.

**Quinone monoxime**, obtained by the action of hydroxylamine hydrochloride on quinone (*H. Goldschmidt*, B., 1884, 213), is identical with the compound obtained by the action of nitrous acid on phenol, or by the hydrolysis of *p*-nitroso-dimethyl-aniline, and previously termed *p*-nitroso-phenol. It would appear to have the oxime constitution  $\text{O}:\text{C}_6\text{H}_4:\text{N}\cdot\text{OH}$ , as with hydroxylamine it yields the dioxime  $\text{OH}\cdot\text{N}:\text{C}_6\text{H}_4:\text{N}\cdot\text{OH}$ , and when alkylated yields ethers of the type  $\text{O}:\text{C}_6\text{H}_4:\text{N}\cdot\text{OR}$ .

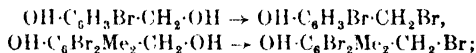
**Quinone monanil** is obtained by oxidizing *p*-hydroxy-diphenylamine,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{C}_6\text{H}_5$ , and forms fiery-red crystals

melting at  $97^{\circ}$ ; with aniline it yields dianilino-quinone anil,  $\text{O}:\text{C}_6\text{H}_2(\text{NPh})_2:\text{NPh}$ . The dianil is obtained by oxidizing diphenyl-*p*-phenylene-diamine,  $\text{C}_6\text{H}_4(\text{NPh})_2$ ; it melts at  $175^{\circ}$ – $180^{\circ}$ , and its dianilide, viz. dianilino-quinone dianil,  $\text{NPh}:\text{C}_6\text{H}_2(\text{NPh})_2:\text{NPh}$ , is most readily obtained by heating *p*-nitroso-dimethyl-aniline with aniline and aniline hydrochloride.

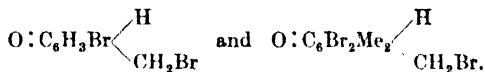
The dyes known as indophenols and indamines are derivatives of quinone-anils (see Chap. LIX, G.).

### G. Pseudo-phenols. Methylene-quinones

Numerous phenolic alcohols react with halogen hydracids yielding the corresponding esters of the alcohols, e.g.:



but the products thus obtained are insoluble in alkalis, and are characterized by the reactivity of the bromine atom in the  $\cdot\text{CH}_2\text{Br}$  group. The compounds have been termed by *Auwers* **pseudo-phenols**, and they are usually regarded as *o*- or *p*-quinone derivatives, e.g.:



Such compounds readily react with alkalis, losing hydrogen bromide and yielding **methylene-quinones** or **quinomethanes** of the type  $\text{O}:\text{C}_6\text{H}_3\text{Br}:\text{CH}_2$ ; the majority of these are unstable, and immediately yield condensation products which are insoluble in alkalis (cf. *Auwers*, A., **301**, 203; B., 1899, 2978; 1901, 4256; 1903, 1878; 1906, 435; *Zincke*, A., **320**, 145; **322**, 174; **329**, 1; **353**, 335, 357).

A series of **quinodimethane** compounds has been isolated, e.g.  $\text{CPh}_2:\text{C}_6\text{H}_4:\text{CPh}_2$ , **tetraphenylquinodimethane**, yellow crystals, m.-pt.  $268^{\circ}$  (*Tschitschibabin*, B., 1908, **41**, 2770);  $\text{C}_{10}\text{H}_7\text{CPh}:\text{C}_6\text{H}_4:\text{CH}_2$ , a dark-blue powder (*Schlenk* and *Meyer*, B., 1919, **52**, B, 8).

## XXVI. AROMATIC ACIDS

The aromatic acids are analogous to the fatty acids. As acids they form metallic salts, esters, chlorides, anhydrides, amides, &c.:

$C_6H_5 \cdot CO_2H$  (benzoic acid).

$C_6H_5 \cdot CO_2C_2H_5$  (ethyl benzoate);  $(C_6H_5 \cdot CO)_2O$  (benzoic anhydride);

$C_6H_5 \cdot CO \cdot Cl$  (benzoyl chloride);  $C_6H_5 \cdot CO \cdot NH_2$  (benzamide); &c.

As benzene derivatives they yield chloro-, bromo-, iodo-, hydroxy-, nitro-, amino-, and sulphonic acid derivatives, &c., e.g.:

$C_6H_4Cl \cdot CO_2H$  (chloro-benzoic acids);

$NH_2 \cdot C_6H_4 \cdot CO_2H$  (amino-benzoic acids);

$OH \cdot SO_2 \cdot C_6H_4 \cdot CO_2H$  (sulpho-benzoic acids);

$OH \cdot C_6H_4 \cdot CO_2H$  (hydroxy-benzoic acids);

$C_6H_5 \cdot CH(OH) \cdot CO_2H$  (mandelic acid); &c.

*Constitution.*—Corresponding with the aromatic acids there are nitriles, e.g. with benzoic acid, benzo-nitrile,  $C_6H_5 \cdot C \cdot N$ , which may also be regarded as cyanogen derivatives of the hydrocarbons (in the above case, cyano-benzene), and which, on hydrolysis, yield the acids. From this, and from their general properties, it follows that their constitution must correspond exactly with that of the fatty acids; like the latter they are characterized by the presence of carboxyl,  $CO \cdot OH$ , in the molecule. There are monobasic, di-, tri-, and up to hexabasic aromatic acids, according to the number of hydrogen atoms in the molecule which are readily replaceable by metallic radicals, i.e. according to the number of carboxyl groups.

Numerous unsaturated aromatic acids are known. As unsaturated compounds, they readily form additive compounds with hydrogen, chlorine, hydrogen iodide, and are thereby converted into saturated acids or their substitution products. In most of these additions the benzene nucleus remains unaltered. Their constitution is therefore entirely analogous to that of the acids of the acrylic or propiolic series; they contain a side chain with a double or triple carbon bond:

$C_6H_5 \cdot CH : CH \cdot CO_2H$   
Cinnamic acid

$C_6H_5 \cdot C \equiv C \cdot CO_2H$ .  
Phenyl-propionic acid

In addition to the aromatic acids proper, other acids are known, *which are derivatives either of a completely reduced or a partially reduced benzene molecule*. The acids of the former series, e.g. the hexa-hydro-benzoic acids, have properties very similar to those of the saturated fatty acids; while those of the latter, e.g. the di- and tetrahydro-benzoic acids, resemble the unsaturated fatty acids (cf. p. 409).

The aromatic hydroxy-acids, e.g. the hydroxy-benzoic acids, which are both phenols and acids, manifestly contain phenolic hydroxyl (i.e. hydroxyl which is linked directly to the benzene nucleus) in addition to the carboxyl group or groups; they are capable of yielding salts either as acids or as phenols, but otherwise they correspond in many points with the aliphatic hydroxy-acids.

The true aromatic hydroxy-acids, such as mandelic acid (phenyl-glycollic acid), which correspond completely with the aliphatic hydroxy-acids, contain their alcoholic hydroxyl not in the benzene nucleus, but in the side chain, as is also the case with the aromatic alcohols.

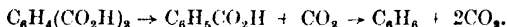
*Nomenclature.*—One of the simplest systems of nomenclature is the designation of the aromatic acids as carboxylic acids of the original hydrocarbons in question, e.g. phthalic acid is benzene-1 : 2-dicarboxylic acid. Many names, such as xylic acid, are taken from those of the hydrocarbons into which the carboxyl has entered, while others, such as mesitylenic acid, indicate the hydrocarbons from which the acids are obtained by oxidation. An important principle as regards nomenclature depends upon the fact that aromatic acids can be derived from almost every fatty acid of any consequence by the exchange of H for  $C_6H_5$ , e.g.:



Similarly, phenylated glycollic, succinic, malic, and tartaric series are known. Thus atropic acid,  $C_6H_5 \cdot C(CO_2H) : CH_2$ , is  $\alpha$ -phenyl-acrylic acid, and cinnamic acid,  $C_6H_5 \cdot CH : CH \cdot CO_2H$ ,  $\beta$ -phenyl-acrylic acid.

*Properties.*—Most of the aromatic acids are solid crystalline substances, generally only sparingly soluble in water, and therefore precipitated by acids from solutions of their salts, but often readily soluble in alcohol and ether. The simpler among them can be distilled or sublimed without decom-

position, while the more complicated, especially phenolic and polycarboxylic acids, evolve carbon dioxide when heated; e.g. salicylic acid,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H}$ , breaks up into phenol and  $\text{CO}_2$ . The elimination of carbonic anhydride from those acids which volatilize without decomposition may be effected by heating with soda-lime; in polybasic acids the carboxyls may be successively decomposed:



*Occurrence.*—A large number of the aromatic acids are found in nature, e.g. in many resins and balsams, and also in the animal organism in the form of nitrogenous derivatives such as hippuric acid (benzoyl-glycocoll),  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ .

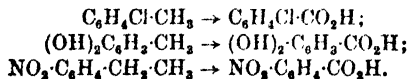
*Modes of Formation.*—A. Of the **saturated** acids:

1. By the oxidation of the corresponding primary alcohols or aldehydes, e.g. benzoic acid from benzyl alcohol, or from benzaldehyde. Benzaldehyde can be oxidized by atmospheric oxygen, but the primary product appears to be a *per-acid*,  $\text{Ph}\cdot\text{CO}\cdot\text{O}\cdot\text{OH}$ , which then reacts with a second mol. of aldehyde forming 2 mols. of benzoic acid. By oxidizing in presence of  $\text{Ac}_2\text{O}$  it is possible to isolate a compound  $\text{Ph}\cdot\text{CO}\cdot\text{O}\cdot\text{OAc}$  (B., 1900, 1581).

2. One of the commonest methods of obtaining aromatic acids is by the oxidation of benzene homologues. Each alkyl group present in the nucleus of the hydrocarbon can be oxidized to a carboxylic group, whether it be long or short, e.g. both  $\text{C}_6\text{H}_5\cdot\text{CH}_3$  and  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_3$  yield  $\text{C}_6\text{H}_5\cdot\text{CO}_2\text{H}$ .

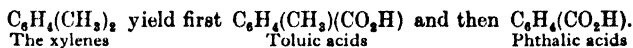
All substituted benzene homologues which contain the substituent in the side chain are similarly oxidized to non-substituted aromatic acids, e.g.  $\text{C}_6\text{H}_5\cdot\text{CH}_2\text{Cl}$ ,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{NH}_2$ , and  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$  yield  $\text{C}_6\text{H}_5\cdot\text{CO}_2\text{H}$ .

A substituted benzene homologue which contains halogen, nitro-, sulpho-, amino-, hydroxy-, &c., substituents attached to the benzene nucleus, yields a similarly substituted aromatic acid, e.g.:



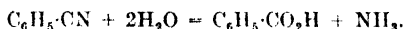
Should there be several side chains in the molecule, they are usually all converted directly into carboxyl by chromic

acid; whereas by using dilute nitric acid, this transformation can be effected step by step, e.g.:

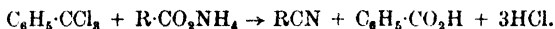


Nevertheless, the three classes of isomeric benzene derivatives with two side chains comport themselves differently. The *para*-compounds are the most readily oxidized to acids by chromic acid mixture, and then the *meta*-; whereas the *ortho*-compounds are either completely destroyed by it (p. 409), or not attacked at all. The last-named may, however, be oxidized in the normal manner by nitric acid or potassic permanganate. The entrance of a negative group or of hydroxyl into the *o*-position with respect to the alkyl radical renders the oxidation more difficult.

3. By the hydrolysis of the corresponding nitriles:

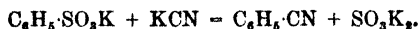


These **nitriles**, which can be prepared from the ammonium salts of the acids by the elimination of water, ( $2\text{H}_2\text{O}$ ) by the action of (1)  $\text{PCl}_3$  or  $\text{POCl}_3$  in the presence of pyridine; (2) *p*-Toluene-sulphonyl chloride; (3)  $\text{C}_6\text{H}_5\cdot\text{CCl}_3$ , e.g.:

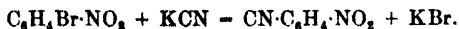


Nitriles are also obtained by the following syntheses:

(a) By distilling the potassium salts of the sulphonic acids with potassium cyanide or ferrocyanide (*Merz*), just as the nitriles of the fatty acids are formed from the potassium alkyl-sulphates (p. 108):

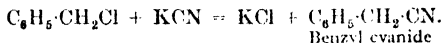


Formation of nitriles is not effected by boiling the aryl halide with KCN solutions, but occurs at  $200^\circ$  (B., 1919, 1749) and is favoured by certain catalysts, e.g. bromides of Cu, Ni and Co. The halogen is more readily replaced by cyanogen if sulphonic acid or nitro-groups are also present:

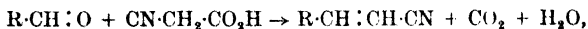


Benzyl chloride,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\text{Cl}$ , and all hydrocarbons halogenated in the side chain, on the other hand, react with potas-

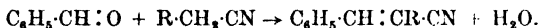
sium cyanide in the manner characteristic of the aliphyl halides:



(b) Unsaturated nitriles are formed by the condensation of aryl aldehydes with cyanoacetic acid:

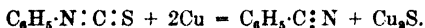


or by condensing the aldehyde with an alkyl cyanide and NaOEt:



(c) By diazotizing the primary amines and replacing the diazo-group by cyanogen, according to *Sandmeyer's* reaction (Chap. XXII, A.). In some cases improved yields are obtained by using alkali cupridiammonium cyanide or potassium cyanide and nickel chloride. This reaction is frequently made use of in the preparation of substituted benzo-nitriles, e.g. 2:4-dibromobenzo-nitrile,  $\text{C}_6\text{H}_3\text{Br}_2\text{CN}$ , and the isomeric 2:6-compound, also of tolunitriles,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CN}$ .

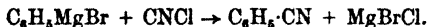
(d) By heating the mustard oils (phenyl-iso-thiocyanates, Chap. XII, D.) with copper or zinc dust (*Weith*):



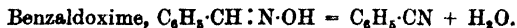
(e) By the molecular transformation of the isomeric isonitriles at a somewhat high temperature:



(f) By the action of cyanogen or cyanogen chloride on organo-magnesium halides:

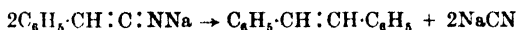


(g) By eliminating the elements of water from the oximes of the aldehydes by means of acetyl chloride (Chap. L, C1):



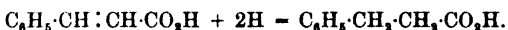
(h) Nitriles of the type  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CN}$  contain a reactive methylene group and give rise to sodium derivatives, e.g.  $\text{C}_6\text{H}_5\cdot\text{CHNa}\cdot\text{CN}$  or  $\text{C}_6\text{H}_5\cdot\text{CH}\cdot\text{C}\cdot\text{NNa}$ , which can be alkylated, e.g.  $\text{C}_6\text{H}_5\cdot\text{CHEt}\cdot\text{CN}$ , and ultimately  $\text{C}_6\text{H}_5\cdot\text{CEt}_2\cdot\text{CN}$ .

The sodium compound when heated out of contact with air gives stilbene:

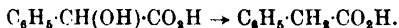


(*Rising*, J. A. C. S., 1928, 1699; 1929, 262).

4. By the reduction of unsaturated acids, thus hydrocinnamic by the reduction of cinnamic acid with sodium amalgam and water, or with hydrogen and finely divided palladium:

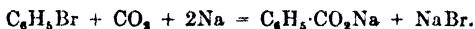


The acids obtained by this method always contain the  $\text{CO}_2\text{H}$  group attached to a side chain. Similar acids can also be obtained by the reduction of hydroxy-, bromo-, or keto-acids, where the OH, Br, CO, and  $\text{CO}_2\text{H}$  are all in side chains, e.g.:

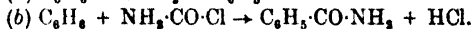
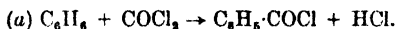


5. A number of methods of introducing  $\text{CO}_2\text{H}$  into the benzene nucleus can be effected by means of carbonic acid derivatives. In many cases the yields are only small, and the reactions are mainly of theoretical interest.

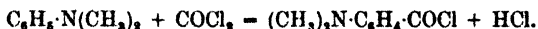
(a) Benzoic acid and its homologues are produced by the action of carbon dioxide upon bromo-benzenes, &c., in presence of sodium (*Kekulé*):



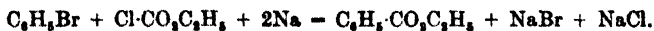
(b) By the action of  $\text{AlCl}_3$  with (a) carbonyl chloride or (b) urea chloride on an aromatic hydrocarbon:



Acid chlorides or amides are first formed, but can be readily decomposed by alkali. By the further action of the chlorides upon benzene in presence of  $\text{AlCl}_3$ , ketones are formed (see Benzo-phenone). Carbonyl chloride reacts most readily with tertiary amines:



(c) By the action of sodium upon a mixture of a brominated benzene and ethyl chloro-formate (*Wurtz*); in this case the esters are first formed, but these are readily hydrolysed:



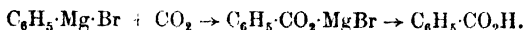


(d) By heating the sulphonates with sodium formate (V. Meyer):



**Phenolic Acids:** The presence of OH groups renders the nucleus more reactive so that hydroxy acids (usually *para*) can be formed by a variety of methods.

(e) By the action of carbon dioxide on ethereal solutions of organo-magnesium compounds (*Grignard's* reagents), and subsequent treatment with acids:

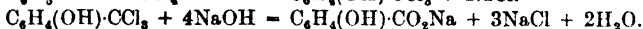


(f) By passing carbon dioxide over heated sodium phenates (*Kolbe*; see Salicylic Acid, this Chap., A3):



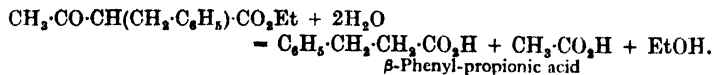
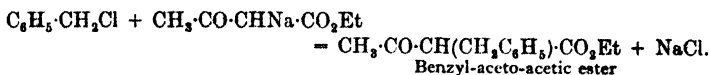
In the case of the polyhydroxy-phenols, e.g. resorcinol, an acid is often formed by merely heating the phenol with a solution of ammonium carbonate or potassium bicarbonate.

(g) By the action of carbon tetrachloride upon phenols in alkaline solution (*Tiemann-Reimer* reaction, Chap. XXV, D.):



6. Syntheses by the aid of ethyl aceto-acetate and ethyl malonate.

Ethyl aceto-acetate reacts with the halide derivatives which are substituted in the side chain, e.g. benzyl chloride, exactly as in the fatty series, with the formation of the more complicated ketonic acids, which again are capable of undergoing either the "acid hydrolysis" or the "ketonic hydrolysis" (p. 259), e.g.:



Ethyl phloroglucinol-dicarboxylate,  $(\text{OH})_3\cdot\text{C}_6\text{H}(\text{CO}_2\text{Et})_2$ , may be synthesized by heating ethyl sodio-malonate with ethyl malonate at  $145^\circ$  (*Moore*, J. C. S., 1904, 165).

7. Hydroxy acids, with OH in the side chain, and keto-

acids are formed by exactly the same methods as in the fatty series (Chap. IX, A.); e.g. mandelic acid by the combination of hydrogen cyanide with benzaldehyde, and hydrolysis of the nitrile thus formed:



or from phenyl-chloro-acetic acid:



B. The following are some of the commoner methods employed for the preparation of **unsaturated** acids:

1. From the mono-haloid substitution products of the saturated acids by the elimination of halogen hydracid, (cf. p. 188); also from the corresponding nitriles, primary alcohols, &c., as in the case of the saturated compounds.

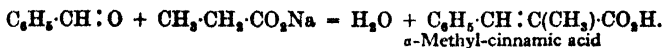
2. According to the *Perkin* synthesis (1877), by the action of aromatic aldehydes upon the sodium salts of fatty acids in the presence of a condensing agent, usually acetic anhydride. Thus, when benzaldehyde is heated with acetic anhydride and sodium acetate, cinnamic acid is formed:



The acetic anhydride probably acts as a dehydrating agent in this instance, the reaction taking place between the sodium acetate and the aldehyde (cf. A., 216, 101). Hydroxy acids are formed as intermediate products by a reaction similar to the "aldol condensation" (p. 154); in the above case, for instance,  $\beta$ -phenyl-hydracrylic acid,  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ .

When the sodium salt and the anhydride of two different acids, e.g. sodium propionate and acetic anhydride, are used, the product varies with the conditions (B., 1901, 918), but usually consists of a mixture of two unsaturated acids.

This reaction also takes place with the halogenated and nitrobenzaldehydes, with the homologues of acetic acid, and also with dibasic acids, e.g. malonic; but all acids employed must contain a  $\text{CH}_2$  group in the  $\alpha$ -position with respect to the  $\text{CO}_2\text{H}$ , as  $\beta$  or  $\gamma$   $\text{CH}_2$  groups do not react:

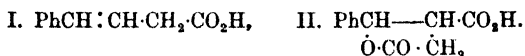


With *o*-hydroxy aldehydes ring formation occurs; cf. Coumarin.

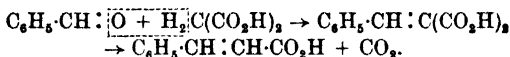
It is a very general method used for the preparation of

$\alpha:\beta$ -unsaturated acids; in certain cases, e.g.  $\alpha$ -phenyl-cinnamic acid,  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{C}(\text{C}_6\text{H}_5)\cdot\text{CO}_2\text{H}$ , and its nitro-derivatives, two stereo-isomerides are produced corresponding with the two crotonic acids or with fumaric and maleic acid.

When sodium succinate is used in place of sodium acetate the product is a mixture of phenylisocrotonic acid I and phenylparaconic acid II:



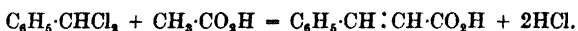
Unsaturated mono- and dibasic acids are also formed when aromatic aldehydes are heated with malonic acid in presence of ammonia, aniline, or other amines (*Knoevenagel*):



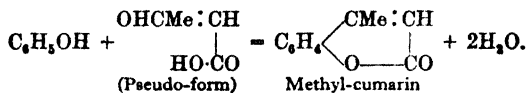
The esters of these acids are formed when aromatic aldehydes are condensed with the esters of fatty acids in the presence of sodium ethoxide (*Claisen*, B., 1890, 976; cf. *Claisen*, condensation, p. 257).

Aldehydes react very readily with ethyl malonate or ethyl cyanoacetate in presence of a few drops of a secondary base, e.g. piperidine or dimethylamine, the products being esters of unsaturated acids (*Knoevenagel*).

3. Cinnamic acid is also formed by the action of benzal chloride upon sodium acetate (*Caro*):



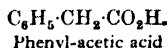
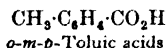
4. Ethyl acetoacetate and phenols react in the presence of concentrated  $\text{H}_2\text{SO}_4$ , yielding unsaturated phenolic acids or their anhydrides, e.g.:



## A. Monobasic Aromatic Acids

*Constitution and Isomers.*—The cases of isomerism in the aromatic acids are easy to tabulate. An isomer of benzoic acid is neither theoretically possible nor actually known.

Carboxylic acids of the formula  $C_8H_8O_2$  may, however, be derived from toluene by the entrance of carboxyl either into the benzene nucleus or into the side chain:



The nature of their oxidation products yields proof of their constitution, the former yielding the phthalic acids and the latter benzoic.

A large number of isomeric acids,  $C_9H_{10}O_2$ , are known. Hydrocinnamic acid and hydratropic acid are phenyl-propionic acids, the former  $\beta$ - and the latter  $\alpha$ -, corresponding with the lactic acids. The tolyl acetic acids,  $CH_3 \cdot C_6H_4 \cdot CH_2 \cdot CO_2H$ , and the ethyl-benzoic acids,  $C_2H_5 \cdot C_6H_4 \cdot CO_2H$ , yield phthalic acids when oxidized. Lastly, mesitylenic acid and its isomers are dimethyl-benzoic acids, and are oxidizable to benzene-tricarboxylic acids.

The unsaturated acids, cinnamic and atropic acids, are structurally isomeric and correspond with  $\beta$ - and  $\alpha$ -chloracrylic acids (p. 193), whereas cinnamic and allo-cinnamic acids are stereo-isomeric.

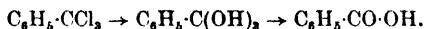
The hydroxy-toluic acids,  $C_6H_3(CH_3)(OH)(CO_2H)$ , are isomeric with mandelic acid,  $C_6H_5 \cdot CH(OH) \cdot CO_2H$ , the former being oxidized to hydroxy-phthalic acids,  $C_6H_3(OH)(CO_2H)_2$ , and the latter to benzoic acid; the hydrocoumaric acids,  $C_9H_{10}O_3$ , are isomeric with tropic acid. The first-named yield hydroxy-benzoic acids on oxidation, and the last benzoic.

## 1. MONOBASIC SATURATED ACIDS

**Benzoic acid**,  $C_6H_5 \cdot CO_2H$ , was discovered in gum benzoin in 1608, and prepared from urine by *Scheele* in 1785. Its composition was established by *Liebig* and *Wöhler's* classical researches in 1832. It occurs in nature in gum benzoin, from which it may be obtained by sublimation ("acidum benzoicum ex resina"); also in dragon's-blood (a resin), in Peru and Tolu balsams, in castoreum, and in cranberries. It is present in the urine of horses in combination with glyccoll as hippuric acid, from which it may be obtained by hydrolysis with hydrochloric acid ("acidum benzoicum ex urina"). It is obtained on the large scale ("ac. benz. ex toluole") as a by-product in the manufacture of oil of bitter almonds from

SATURATED ACIDS					M.-pt.	K × 10 <sup>4</sup>	M.-pt. of Amide
Benzoic	..	..	..	C <sub>6</sub> H <sub>5</sub> ·CO <sub>2</sub> H	121°	0.63	128°
Phenyl-acetic	..	..	..	C <sub>6</sub> H <sub>5</sub> ·CH <sub>2</sub> ·CO <sub>2</sub> H	76	0.55	154
<i>o</i> -Toluic	..	..	..	CH <sub>3</sub> ·C <sub>6</sub> H <sub>4</sub> ·CO <sub>2</sub> H	105	1.2	139
<i>m</i> -Toluic	..	..	..	Do.	110	0.54	94
<i>p</i> -Toluic	..	..	..	Do.	177	0.43	159
Hydrocinnamic	..	..	..	C <sub>6</sub> H <sub>5</sub> ·CH <sub>2</sub> ·CH <sub>2</sub> ·CO <sub>2</sub> H	48	0.23	105
Hydratropic	..	..	..	CH <sub>3</sub> ·CH(C <sub>6</sub> H <sub>5</sub> )·CO <sub>2</sub> H	liq.	0.42	92
<i>o</i> -Tolyl-acetic	..	..	..	CH <sub>3</sub> ·C <sub>6</sub> H <sub>4</sub> ·CH <sub>2</sub> ·CO <sub>2</sub> H	89	—	161
<i>m</i> -Tolyl-acetic	..	..	..	Do.	61	—	141
<i>p</i> -Tolyl-acetic	..	..	..	Do.	91	—	184
<i>o</i> -Ethyl-benzoic	..	..	..	C <sub>2</sub> H <sub>5</sub> ·C <sub>6</sub> H <sub>4</sub> ·CO <sub>2</sub> H	68	—	152
<i>m</i> -Ethyl-benzoic	..	..	..	Do.	47	—	—
<i>p</i> -Ethyl-benzoic	..	..	..	Do.	112	—	115
Mesitylenic acid	..	..	..	(CH <sub>3</sub> ) <sub>2</sub> ·C <sub>6</sub> H <sub>3</sub> ·CO <sub>2</sub> H <sub>1</sub>	166	—	133
HYDROXY-SATURATED ACIDS							
Salicylic acid (ortho)	..	..	..	OH·C <sub>6</sub> H <sub>4</sub> ·CO <sub>2</sub> H	155	10.2	140
<i>m</i> -Hydroxy-benzoic acid	..	..	..	Do.	200	0.83	—
<i>p</i> -Hydroxy-benzoic acid	..	..	..	Do.	214	0.29	—
<i>p</i> -Methoxy-benzoic or anisic acid	..	..	..	CH <sub>3</sub> ·O·C <sub>6</sub> H <sub>4</sub> ·CO <sub>2</sub> H	184	0.32	162-163
Mandelic acid	..	..	..	C <sub>6</sub> H <sub>5</sub> ·CH(OH)·CO <sub>2</sub> H	118	4.2	132
Tropic acid	..	..	..	C <sub>6</sub> H <sub>5</sub> ·CH(CH <sub>2</sub> ·OH)·CO <sub>2</sub> H	117	0.75	—
UNSATURATED ACIDS							
Cinnamic acid	..	..	..	C <sub>6</sub> H <sub>5</sub> ·CH:CH·CO <sub>2</sub> H	133	0.35	141
Atropic acid	..	..	..	CH <sub>2</sub> :C(C <sub>6</sub> H <sub>5</sub> )·CO <sub>2</sub> H	106	1.4	—
Phenyl-propionic acid	..	..	..	C <sub>6</sub> H <sub>5</sub> ·C: C·CO <sub>2</sub> H	136	59.0	100
Coumaric or <i>p</i> -hydroxy-cinnamic acid	..	..	..	OH·C <sub>6</sub> H <sub>4</sub> ·CH:CH·CO <sub>2</sub> H	206	0.26	—

benzyl chloride or benzal chloride. The acid may also be formed by heating benzo-trichloride with water to a somewhat high temperature:



Benzoic acid is also present in coal-tar. It crystallizes in colourless glistening plates or flat needles, sublimes readily, and is volatile with steam; its vapour has a peculiar irritating odour, and gives rise to coughing. It melts at  $121^\circ$ , boils at  $250^\circ$ , and is readily soluble in hot water, but only sparingly in cold. When heated with lime, it is decomposed into benzene and carbon dioxide. It is used in medicine and in the manufacture of aniline blue. Some of its salts crystallize beautifully, e.g. **calcium benzoate**,  $(\text{C}_6\text{H}_5\cdot\text{CO}_2)_2\text{Ca} + 3\text{H}_2\text{O}$ , in glistening prisms.

From the partially or wholly reduced benzene molecule there are derived (a) the **dihydro-benzoic acids**,  $\text{C}_6\text{H}_7\cdot\text{CO}_2\text{H}$ , of which five are theoretically possible, according to the position of the double linkings, viz.  $\Delta$ -1 : 3-,  $\Delta$ -1 : 4-,  $\Delta$ -1 : 5-,  $\Delta$ -2 : 4-, and  $\Delta$ -2 : 5-dihydro-benzoic acids, but only two known (B., 1891, 2623, and 1893, 454); (b) the **tetrahydro-benzoic acids**,  $\text{C}_6\text{H}_9\cdot\text{CO}_2\text{H}$ , all three of which are actually known, viz.  $\Delta$ -1-,  $\Delta$ -2-, and  $\Delta$ -3-tetrahydro-benzoic acids (A., 271, 231); and a **hexahydro-benzoic acid**,  $\text{C}_6\text{H}_{11}\cdot\text{CO}_2\text{H}$  (*cyclo-hexane-carboxylic acid*), which is found in the petroleum from Baku, and which can also be prepared from benzoic acid.

The **Esters**, e.g. **methyl benzoate**,  $\text{C}_6\text{H}_5\cdot\text{CO}_2\text{CH}_3$ , b.-pt.  $199^\circ$ , and **ethyl benzoate**,  $\text{C}_6\text{H}_5\cdot\text{CO}_2\text{C}_2\text{H}_5$ , b.-pt.  $213^\circ$ , are always prepared by the catalytic method of esterification (Chap. VII, A.), namely, by boiling the acid for three to four hours with a 3 per cent solution of dry hydrogen chloride or of concentrated sulphuric acid in the requisite alcohol (*E. Fischer and Speier*, B., 1895, 3252). They may also be obtained by the other general methods for the preparation of esters: (a) by the action of an acid chloride on the alcohol alone, or in presence of alkali (*Schotten, Baumann*) or of pyridine (*Einhorn and Hollandt*); (b) by the action of an alkyl iodide on the silver salt of the acid; and (c) by the action of alkyl sulphates, more especially methyl sulphate, on aqueous solutions of the alkali salts of the acids (*Werner and Seybold*, B., 1904, 3658). These esters are liquids of pleasant aromatic odour, used in perfumery, boil for the most part without decomposition, and

frequently serve for the recognition and estimation of alcohols. They may be hydrolysed in much the same manner as the aliphatic esters, although as a rule not so readily.

**Benzyl benzoate**,  $C_6H_5 \cdot CO_2 \cdot CH_2 \cdot C_6H_5$ , is present in the balsams of Peru and Tolu.

**Benzoyl chloride**,  $C_6H_5 \cdot CO \cdot Cl$  (*Liebig* and *Wöhler*), obtained by the action of phosphorus pentachloride on the acid, is the complete analogue of acetyl chloride, but more stable than the latter, since it is only slowly hydrolysed by cold water, although quickly by hot. It is a colourless liquid boiling at  $198^\circ$ , and has a most characteristic pungent odour. It is prepared technically by chlorinating benzaldehyde.

**Benzoic anhydride**,  $(C_6H_5 \cdot CO)_2O$  (*Gerhardt*), analogous to acetic anhydride, is prepared from benzoic acid and acetic anhydride (*Org. Synth.*, 1923, 21). It crystallizes in prisms insoluble in water, boils without decomposition, and becomes hydrated on boiling with water. M.-pt.  $39^\circ$ .

In addition to the ordinary anhydrides or oxides, peroxides of the type **benzoyl peroxide** or **benzo-peroxide**,  $C_6H_5 \cdot CO \cdot O \cdot O \cdot CO \cdot C_6H_5$ , are known. They may be obtained by the action of the acid chloride on a cooled solution of sodium peroxide (*B.*, 1900, 1575, and *C. C.*, 1899, 2, 396). Benzo-peroxide crystallizes from alcohol in prisms, melts at  $106^\circ$ – $108^\circ$ , is relatively stable, and is insoluble in water. When its ethereal solution is mixed with sodium ethoxide, the products formed are ethyl benzoate, and the sodium salt of **perbenzoic acid**,  $C_6H_5 \cdot CO \cdot O \cdot OH$ , a hygroscopic acid melting at  $41^\circ$ – $43^\circ$ . It has a strong odour resembling hypochlorous acid, is readily volatile, but decomposes violently when heated, and is a strong oxidizing agent; for example, for converting ethylene compounds into ethylene oxides (p. 221). Many aliphatic and aromatic acids yield similar derivatives.

**Benzamide**,  $C_6H_5 \cdot CO \cdot NH_2$ , is prepared from benzoyl chloride and ammonia or ammonium carbonate. It forms lustrous, nacreous plates, melting at  $130^\circ$ , boils without decomposition, and is readily soluble in hot water.

The amido-hydrogen of benzamide may be substituted by alkyl radicals such as phenyl, &c., with the formation, e.g., of **benzanilide**,  $C_6H_5 \cdot CO \cdot NHC_6H_5$ , the anilide of benzoic acid, a compound which can be readily prepared from aniline and benzoic acid, or aniline and benzoyl chloride. It crystallizes in colourless plates, melts at  $158^\circ$ , distils unchanged, and is

the analogue of acetanilide, but is more difficult to hydrolyse, fusion with potash being one of the best methods.

**Thio-benzamide**,  $C_6H_5 \cdot CS \cdot NH_2$ , is obtained by the union of benzo-nitrile with hydrogen sulphide, or by heating benzylamine with sulphur.

**Benzoyl-hydrazine**, *Benzhydrazide*,  $C_6H_5 \cdot CO \cdot NH \cdot NH_2$ , obtained from ethyl benzoate and hydrazine hydrate, melts at  $112^\circ$ , and with nitrous acid yields **benzoyl-azimide**, *benzazide*,

$C_6H_5 \cdot CO \cdot N \begin{smallmatrix} \nearrow N \\ \searrow N \end{smallmatrix}$ , which yields benzoic and hydrazoic acids on hydrolysis (Curtius, 1895).

Metallic derivatives of benzamide are also known, e.g. **benzamide silver** (Titherley, J. C. S., 1897, 468; 1901, 407) which exists in two forms: a white stable compound,  $C_6H_5 \cdot C(OAg) : NH$ , and an unstable orange compound,  $C_6H_5 \cdot CO \cdot NHAg$ .

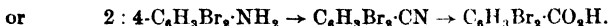
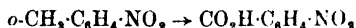
**Hippuric acid**, *Benzamino-acetic acid*,  $C_6H_5 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$ , is an amino-derivative of benzoic acid, being derived from the latter and glycoll (amino-acetic acid); it may be prepared by heating benzoic anhydride with glycoll, and is present in the urine of horses and of other herbivora. When benzoic acid or toluene is taken internally, it is eliminated from the system in the form of hippuric acid. It crystallizes in rhombic prisms, sparingly soluble in cold water but readily in hot, decomposes when heated, and forms salts, esters, nitro-derivatives, &c. When hydrolysed with concentrated hydrochloric acid it yields glycoll hydrochloride and benzoic acid.

**Benzo-nitrile**,  $C_6H_5CN$  (cf. p. 507), is an oil which smells like oil of bitter almonds, and boils at  $191^\circ$ . It possesses all the properties of a nitrile, combining slowly with nascent hydrogen to benzylamine, readily with halogen hydride to an imino-chloride, with amines to amidines, with hydroxylamine to amidoximes (cf. Chap. VII, H.). With hydrogen peroxide it yields benzamide.

**Substituted Benzoic Acids.**—The hydrogen atoms of benzoic acid are replaceable by halogen with the formation, e.g., of **chloro-benzoic acid**,  $C_6H_4Cl \cdot CO_2H$ . In such formation of mono-substitution products the halogen takes up the meta-position with respect to the carboxyl. Nitric acid (especially a mixture of nitric and sulphuric acids) nitrates it readily, **m-nitro-benzoic acid** being the chief product, together with a smaller quantity of the ortho- and a very little of the para-acid.



The *o*- and *p*-halogen and nitro-compounds are usually prepared by indirect methods, e.g.:



#### SUBSTITUTED BENZOIC ACIDS

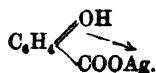
Acid		M.-pt.	$K \times 10^5$	Methyl ester	
				M.-pt.	B.-pt.
Benzoic ..	— —	121°	6.27	—	199°
<i>o</i> -Methyl-benzoic	— —	105	12.0	—	213
<i>m</i> -Methyl-benzoic	— —	110	5.35	—	215
<i>p</i> -Methyl-benzoic	— —	177	4.24	33°	—
<i>o</i> -Bromo-benzoic	— —	150	145	—	247
<i>m</i> -Bromo-benzoic	— —	155	15.4	31	—
<i>p</i> -Bromo-benzoic	— —	251	10.7	31	—
<i>o</i> -Nitro-benzoic	— —	148	—	30	—
<i>m</i> -Nitro-benzoic	— —	141	32.1	—	—
<i>p</i> -Nitro-benzoic	— —	240	37.6	79	—
<i>o</i> -Amino-benzoic	— —	144	1.0	96	—
<i>m</i> -Amino-benzoic	— —	174	3.0	—	—
<i>p</i> -Amino-benzoic	— —	186	1.0	—	—

The numbers for  $K$  given in the table indicate that the introduction of acylous radicals, e.g.  $\text{NO}_2$ , Br, &c., more especially into the ortho-position, markedly increases the strength of the acid, whereas the introduction of basylous radicals, e.g. the amino-, more especially into ortho-positions, tends to weaken the acid (Chap. VI, D.).

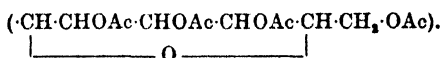
The amino-benzoic acids,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H}$ , which are obtained by the reduction of the nitro-acids with tin and hydrochloric acid, &c., are interesting, as they are both bases and acids, i.e. **amphoteric**, and therefore similar to glycocoll in chemical character; they combine with hydrochloric acid, chloro-platinic acid, &c., as well as reacting with mineral bases to yield metallic salts. With regard to their constitution, cf. Glycocoll, p. 243. With nitrous acid they yield

**diazo-benzoic acids**,  $\text{C}_6\text{H}_4\begin{matrix} \text{N:N} \\ \diagup \quad \diagdown \\ \text{CO}_2 \end{matrix}$ , which correspond with the diazo-benzene-sulphonic acids (Chap. XXIII).

The salts derived from some amino- and hydroxy-benzoic acids are frequently represented by formulæ with a co-ordinate link between the metal of the  $\text{CO}_2\text{M}$  group and the N or O atom, e.g.:



Such a formula accounts to a certain extent for the fact that silver salicylate and tetra-acetobromoglucose (p. 341) yield both  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{COOX}$  and  $\text{OX}\cdot\text{C}_6\text{H}_4\cdot\text{COOH}$ , where X = the tetra-acetylglucose residue



**o-Amino-benzoic acid** is usually prepared from phthalimide,  $\text{C}_6\text{H}_4\begin{array}{c} \text{CO} \\ \diagup \quad \diagdown \\ \text{NH} \end{array}$ , by the *Hofmann* reaction (cf. Amides, behaviour of, par. 5), and is termed **anthranilic acid**; it forms (in contradistinction to the *m*- and *p*-acids) an intramolecular anhydride, **anthranil**,  $\text{C}_6\text{H}_4\begin{array}{c} \text{CO} \\ \diagup \quad \diagdown \\ \text{NH} \end{array}$ , and is an important

intermediate product in the synthesis of indigo. The methyl ester is an important constituent of the essential oil of orange-blossom.

The **sulpho-benzoic acids**,  $\text{OH}\cdot\text{SO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{OH}$ , are dibasic acids. An inner imide of *o*-sulpho-benzoic acid is the sweet substance "**saccharine**",  $\text{C}_6\text{H}_4\begin{array}{c} \text{SO}_2 \\ \diagup \quad \diagdown \\ \text{CO} \end{array}\text{NH}$ , i.e. *o*-sulpho-

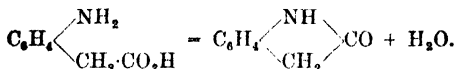
benzimidide, or *o*-benzoyl-sulphone-imide, an imide comparable with succinimide. It is a white crystalline powder, almost three hundred times as sweet as cane-sugar, and is used to some extent in place of the latter, especially with diabetic patients.

**Acids**,  $\text{C}_6\text{H}_5\text{O}_2$ .—1. The three **toluic acids**,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H}$ , can be prepared from the three xylenes. *p*-Toluic acid is obtained from *p*-toluidine, by transforming it—according to the *Sandmeyer* reaction—into *p*-cyano-toluene and hydrolysing the latter. Isomeric with them is:

2. **Phenyl-acetic acid**, *o*-Toluic acid,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  (*Cannizaro*, 1855).—This acid differs characteristically from its isomers by its behaviour upon oxidation (see p. 513). It may be obtained synthetically from benzyl chloride and potassium cyanide, **benzyl cyanide**,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CN}$  (b.pt.  $232^\circ$ ), being formed as intermediate product; it crystallizes in lustrous plates, melts at  $76^\circ$ , and boils at  $262^\circ$ .

It is capable of undergoing substitution either in the benzene nucleus or in the side chain.

**Phenyl-chloroacetic acid**,  $C_6H_5 \cdot CHCl \cdot CO_2H$ , and **phenyl-amino-acetic acid**,  $C_6H_5 \cdot CH(NH_2) \cdot CO_2H$ , correspond with mono-chloroacetic and amino-acetic acids. Isomeric with phenyl-amino-acetic acid are the three **amino-phenyl-acetic acids**,  $NH_2 \cdot C_6H_4 \cdot CH_2 \cdot CO_2H$ , of which the *o*-acid is interesting on account of its close relation to the indigo-group. It does not exist in the free state, but forms an intramolecular anhydride, oxindole (Chap. XII, C.):



The formation of intramolecular anhydrides differentiates ortho-amino-compounds from their *m*- and *p*-isomerides (see Indole). Theoretically, it may take place in the above instance in two different ways, viz. either by the elimination of a hydrogen atom of the amino-group together with OH of the carboxyl, or of both of the amino-hydrogen atoms with the oxygen atom from the carbonyl-group. These two cases are distinguished by *Baeyer* as "**Lactam formation**" and "**Lactim formation**". Oxindole is the lactam of *o*-amino-

phenylacetic acid, isatin,  $C_6H_4 \begin{array}{l} \swarrow NH \\ \searrow CO \end{array} \begin{array}{l} \nearrow CO \\ \nearrow \end{array}$  (Chap. XII, B.), the

lactam of *o*-amino-phenylglyoxylic acid,  $NH_2 \cdot C_6H_4 \cdot CO \cdot CO \cdot OH$ ,

and carbostyryl (Chap. XLIV, A2),  $C_6H_4 \begin{array}{l} \swarrow N \cdot C \cdot OH \\ \searrow CH : CH \end{array}$ , the

lactim of *o*-amino-cinnamic acid.

Both lactams and lactims contain hydrogen which is readily replaceable; in the former case it is present in the amino-group, and in the latter in the hydroxyl.

If the compounds which result from the replacement of hydrogen by alkyl are very stable, the alkyl in them is linked to the nitrogen, and they are derivatives of the lactams; if, on the contrary, they are easily hydrolysed by acids, the alkyl is linked to oxygen, and they are ethers of the lactims. Many lactams and lactims are tautomeric substances (cf. Chap. LIII).

**Acids**,  $C_6H_{10}O_2$ .—1. **Dimethyl-benzoic acids**, *Xylene-carboxylic acids*,  $C_6H_3Me_2 \cdot CO_2H$ . Of these six are possible, and four are known. **Mesitylenic acid**,  $(CO_2H : CH_3 : CH_3 = 1 : 3 : 5)$ , is

prepared by the oxidation of mesitylene. Isomeric with them are—2. The **Phenyl-propionic acids**.

**$\beta$ -Phenyl-propionic acid** or **hydrocinnamic acid**,  $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CO_2H$ , is prepared by reducing cinnamic acid with sodium amalgam, or with hydrogen in presence of colloidal palladium, and is also formed during the decay of albuminous matter. It crystallizes in slender needles; m.-pt.  $48^\circ$ , b.-pt.  $280^\circ$ .

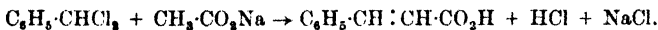
Many substitution products of this acid are known, among which may be mentioned ***o*-nitro-cinnamic acid dibromide**,  $NO_2 \cdot C_6H_4 \cdot CHBr \cdot CHBr \cdot CO_2H$ , a compound nearly related to indigo (Chap. XLI, C.); also,  **$\beta$ -phenyl- $\alpha$ -amino-propionic acid** (phenyl-alanine),  $C_6H_5 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$ , and  **$\beta$ -phenyl- $\beta$ -amino-propionic acid**,  $C_6H_5 \cdot CH(NH_2) \cdot CH_2 \cdot CO_2H$ , both of which can be prepared synthetically; the former is also produced by the degradation of proteins and during the germination of *Lupinus luteus*.

***o*-Amino-hydrocinnamic acid**,  $NH_2 \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot CO_2H$ , is not stable, but is immediately transformed into its lactim, **hydrocarbostyryl** (cf. Quinoline, Chap. XLIV, A2).

**Hydratropic acid**,  **$\alpha$ -Phenyl-propionic acid**,  $CH_3 \cdot CH(C_6H_5) \cdot CO_2H$ , is obtained—as its name implies—by the addition of hydrogen to atropic acid. It is liquid and volatile with steam.

## 2. MONOBASIC UNSATURATED ACIDS

1. **Cinnamic acid**,  $C_6H_5 \cdot CH : CH \cdot CO_2H$  (*Trommsdorf*, 1780), occurs in Peru and Tolu balsams and also in storax, and may be prepared as given at p. 511, but more readily by heating benzal chlorides with anhydrous sodium acetate:



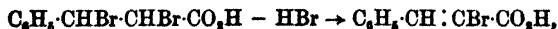
It crystallizes in needles or prisms, dissolves readily in hot water, melts at  $133^\circ$ , and boils at  $300^\circ$ . When fused with potash, it is split up into benzoic and acetic acids; it also yields benzoic acid when oxidized. As an acid it yields salts, esters, &c. Many of the esters are used in perfumery. As an olefine it forms additive compounds, with chlorine, bromine, hydrogen chloride, bromide, iodide, and also with hydrogen and hypochlorous acid, e.g. cinnamic acid dibromide ( **$\beta$ -phenyl- $\alpha$ - $\beta$ -dibromo-propionic acid**),  $C_6H_5 \cdot CHBr \cdot CHBr \cdot CO_2H$ . Further, the hydrogen in the benzene nucleus may be replaced by Cl, Br,  $NO_2$ ,  $NH_2$ , &c.

**Cinnamic Acids.**—According to the ordinary stereo-chemical theory of unsaturated compounds, two cinnamic acids of the formula  $C_6H_5 \cdot CH : CH \cdot CO_2H$  should exist (cf. Maleic and Fumaric Acids, Chap. X, B.). Two have been known for some time, viz. storax-cinnamic acid, melting at  $133^\circ$ , and *allo*-cinnamic acid, melting at  $68^\circ$ , and prepared by reducing  $\beta$ -brom-*allo*-cinnamic acid with zinc and alcohol, or by reducing phenylpropionic acid with hydrogen and finely divided palladium. But, in addition to these, several other cinnamic acids have been described (for summary see *Erlenmeyer*, *Biochem. Zeitsch.*, 1911, **34**, 306). Two of these *iso*-cinnamic melting at  $58^\circ$ – $59^\circ$  (*Liebermann*), and the *iso* acid, m.-pt.  $37^\circ$ – $38^\circ$  (*Erlenmeyer*), and the *allo* acid, m.-pt.  $68^\circ$ , are trimorphous forms of the same substance (*Biilmann*, B., 1909, 182, 1443; 1910, 568). They appear to give the same melt as shown by examination of refractive indices (*Stobbe*), and solubilities (*Meyer*), and also to give the same solutions as shown by their electrical conductivities (*Bjerum*, B., 1910, 571), and absorption spectra (*Stobbe*, *ibid.* 504). Any one of the three acids can be obtained from the melt by impregnating under suitable conditions with a crystal of the desired form.

According to *Stoermer* and *Heymann*, ordinary cinnamic acid has the trans- and the *allo* acid the cis-configuration. This conclusion is based on the fact that the *o*-amino-*allo*-cinnamic acid which yields coumarin (this Chap., A5) when diazotized and boiled with water, and hence the acid in which the benzene nucleus and the  $CO_2H$  group are in cis positions, is the acid which yields *allo*-cinnamic acid when the amino-group is removed. And the isomeric amino-acid which yields *o*-coumaric acid is the one which gives ordinary cinnamic acid (B., 1912, 3099).

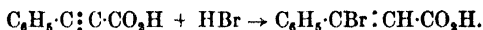
Methyl and ethyl cinnamates are used in the synthetic perfume industry, as are also the esters of many aliphatic and aromatic acids; cf. Thorpe's *Dic. Sup.* II, 126.

Two stereo-isomeric  $\alpha$ -bromo-cinnamic acids and two  $\beta$ -bromo-cinnamic acids have been prepared. The  $\alpha$ -bromo acids are obtained by the elimination of hydrogen bromide from cinnamic acid dibromide:

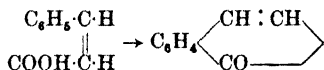


or its esters, and they melt respectively at  $131^\circ$  and  $120^\circ$ .

The corresponding  $\beta$ -acids can be prepared by the addition of hydrogen bromide to phenyl-propionic acid:



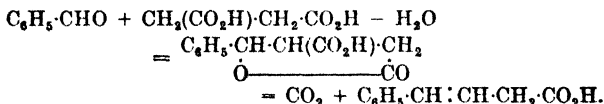
They melt respectively at  $135^\circ$  and  $159^\circ$ . (Compare *Sudborough* and others, J. C. S., 1903, 666, 1153; 1905, 1841; 1906, 105; 1911, 1620.) The two isomerides in each case represent the cis and trans forms. The cis forms are characterized by the readiness with which they yield cyclic indenones in the presence of sulphuric acid, *Liebermann*, B., 1898, 2096:



*o*- and *p*-**Nitro-cinnamic acids**,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ , the first of which is of importance on account of its relation to indigo, are obtained by the nitration of cinnamic acid. On reduction the former yields *o*-**amino-cinnamic acid**, which readily yields its lactim **carbostyryl** ( $\alpha$ -hydroxy-quinoline).

2. **Atropic acid**,  $\text{CH}_2:\text{C}(\text{C}_6\text{H}_5)\cdot\text{CO}_2\text{H}$ , is a decomposition product of atropine. It crystallizes in monoclinic plates, and can be distilled with steam. It breaks up into formic and *o*-toluic acids when fused with potash.

3. ( $\gamma$ )-**Phenyl-isocrotonic acid**, 4-phenyl- $\Delta^3$ -butene-1-acid,  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , is formed when benzaldehyde is heated with sodium succinate and acetic anhydride (*W. H. Perkin, sen.*, also *Jayne*, A., 216, 100):



It is of interest on account of its conversion into  $\alpha$ -naphthol (see this),  $\text{C}_{10}\text{H}_7\cdot\text{OH}$ , upon boiling.

4. **Phenyl-propionic acid**,  $\text{C}_6\text{H}_5\cdot\text{C}:\text{C}\cdot\text{CO}_2\text{H}$  (*Glaser*, 1870), is prepared from cinnamic acid dibromide or its ethyl ester by first converting into  $\alpha$ -brom-cinnamic acid by elimination of hydrogen bromide, and then into the acetylenic acid by further elimination (just as ethylene is converted by bromine into ethylene bromide, and the latter decomposed into acetylene by potash). It crystallizes in long needles, and melts at  $136^\circ$ - $137^\circ$ . When heated with water to  $120^\circ$ , it breaks up into  $\text{CO}_2$  and phenyl-acetylene (p. 414). It can be reduced to

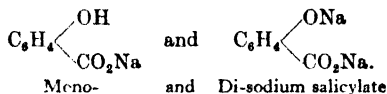
allo-cinnamic acid and then to hydrocinnamic acid and transformed into benzoyl-acetic acid.

***o*-Nitro-phenyl-propionic acid**,  $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C}:\text{C} \cdot \text{CO}_2\text{H}$  (*Baeyer*), is prepared in a manner analogous to that just given, viz. by the addition of bromine to ethyl *o*-nitro-cinnamate and treatment of the resulting dibromide with alcoholic potash (*A.*, 212, 240). It is of interest on account of its relation to indigo (*Chap. XLI, C.*). When heated, it yields *o*-nitrophenyl-acetylene and  $\text{CO}_2$ .

### 3. SATURATED PHENOLIC ACIDS

(For *modes of formation* see p. 510.) These acids may also be obtained by the oxidation of the homologues of phenol and of the hydroxy-aldehydes, which is effected, among other methods, by fusion with alkalis.

The phenolic acids form salts both as carboxylic acids and as phenols, salicylic acid, for instance, the two following classes:



The first of these two salts is not decomposed by  $\text{CO}_2$ , while the second, as the salt of a phenol, is decomposed by it and converted into the first. The phenolic acids behave, therefore, like monobasic acids towards sodium carbonate. When both of the hydrogen atoms are replaced by alkyl, compounds of the type  $\text{C}_2\text{H}_5\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2\text{C}_2\text{H}_5$  are obtained, and these, as both ethers and esters, are only half hydrolysed when boiled with potash, e.g. to  $\text{C}_2\text{H}_5\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CO}_2\text{H}$ , ethyl salicylic acid. The ether acids thus formed are typical monobasic acids, their aliphyl radical being only eliminated by hydriodic acid at a rather high temperature (cf. p. 477).

The *o*-hydroxy acids ( $\text{CO}_2\text{H}:\text{OH} = 1:2$ ) are, in contradistinction to their isomers, volatile with steam, give a violet or blue coloration with ferric chloride, and are readily soluble in cold chloroform.

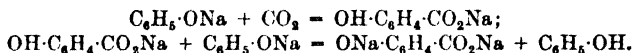
The *m*-hydroxy acids are more stable than the *o*- and *p*-compounds; while most of the latter break up into carbon dioxide and phenols when quickly heated, or when acted on by hydrochloric acid at  $220^\circ$ , the former remain unaltered.

The phenolic acids are much more easily halogenated and

nitrated than the monobasic acids, just as the phenols are far more readily attacked than the benzene hydrocarbons.

**Salicylic acid**, *o*-Hydroxy-benzoic acid ( $\text{CO}_2\text{H}:\text{OH} = 1:2$ ), was discovered by *Piria* in 1839. It occurs in the blossom of *Spiraea Ulmaria*, and as its methyl ester in oil of winter-green, &c. It may be obtained by the oxidation of the glucoside saligenin; by fusing coumarin, indigo, *o*-cresol, &c., with potash; by diazotizing *o*-amino-benzoic acid, &c. (see p. 450).

**Preparation.**—Sodium phenoxide is heated in a stream of carbon dioxide at  $180^\circ$ – $220^\circ$  (*Kolbe*, A., **113**, 125; **115**, 201, &c.), when half of the phenol distils over, leaving disodium salicylate:



When  $\text{C}_6\text{H}_5\text{OK}$  is used, the product is salicylic acid, provided the temperature is kept below  $150^\circ$ ; at higher temperatures, e.g.  $220^\circ$ , the para acid is formed. Mono-potassium salicylate,  $\text{C}_6\text{H}_4(\text{OH})\cdot\text{CO}_2\text{K}$ , decomposes in an analogous manner at  $220^\circ$  into phenol and di-potassium *p*-hydroxy-benzoate.

As *Kolbe's* original method of preparation converted only 50 per cent of the phenol into salicylic acid, *Schmitt* devised the following modification: The sodium phenoxide is heated in a closed vessel with carbon dioxide at  $130^\circ$ , and the compound

first formed,  $\text{C}_6\text{H}_5\cdot\text{O}\cdot\text{C}\begin{smallmatrix} \nearrow \text{ONa} \\ \searrow \text{O} \end{smallmatrix}$ , sodium phenyl-carbonate, is

thus transformed into mono-sodium salicylate by intramolecular rearrangement. (Cf. B., 1905, 1375; A., 1907, **351**, 313; C. C., 1907, ii, 48; also Chap. XXXVIII.)

Salicylic acid crystallizes in colourless four-sided monoclinic prisms, dissolves sparingly in cold water but readily in hot; it melts at  $155^\circ$ , can be sublimed, but is decomposed into phenol and  $\text{CO}_2$  when heated quickly; ferric chloride colours the aqueous solution violet. It is an important antiseptic. It forms two series of salts (the basic calcium salt being insoluble in water), and two series of derivatives, viz.: (1) as an acid it yields chlorides, esters, &c., and (2) as a phenol it yields ethers, &c., e.g. ethyl-salicylic acid,  $\text{C}_6\text{H}_4(\text{OC}_2\text{H}_5)\text{CO}_2\text{H}$ .

**Phenyl salicylate**,  $\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{OPh}$ , the ester derived from phenol and salicylic acid, and generally termed "Salol", is a good antiseptic, and is prepared by the action of an acid chloride such as  $\text{POCl}_3$  or  $\text{COCl}_2$  upon a mixture of salicylic

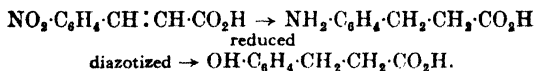


acid and phenol, or by heating the acid itself at 220°. It forms colourless crystals. When its sodium salt is heated to 300°, it undergoes molecular transformation into the sodium salt of the isomeric **phenyl-salicylic acid** (*o*-phenoxybenzoic acid),  $C_6H_5O \cdot C_6H_4 \cdot CO_2Na$ . Other phenols also yield salols, e.g. *p*-acetylaminophenol yields *salophene*.

***m*-Hydroxy-benzoic acid** is prepared by diazotizing *m*-amino-benzoic acid. It crystallizes in microscopic plates, dissolves readily in hot water, and sublimes without decomposition; ferric chloride does not colour its aqueous solution.

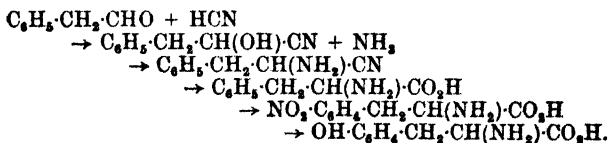
***p*-Hydroxy-benzoic acid** forms monoclinic prisms (+  $H_2O$ ), and ferric chloride gives no coloration with the aqueous solution. As a phenol it yields the methyl ether, **anisic acid**,  $OMe \cdot C_6H_4 \cdot CO_2H$ , prepared by treating *p*-hydroxy-benzoic acid with methyl alcohol, potash and methyl iodide, and saponifying the dimethyl derivative first formed. It is also formed by the oxidation of anisole. It is not a phenolic acid but an ether and a monobasic acid; hydriodic and hydrochloric acids at high temperatures decompose it into *p*-hydroxy-benzoic acid and methyl iodide or chloride.

**Hydro-para-coumaric acid** (1 : 4),  $OH \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot CO_2H$ , *β-p-hydroxy-phenyl-propionic acid*, is produced by the decay of **tyrosine**, *β-hydroxy-phenyl-alanine*,  $OH \cdot C_6H_4 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$ , and also synthetically from *p*-nitro-cinnamic acid:



Tyrosine, which crystallizes in fine silky needles, is found in old cheese (*τυρός*), in the pancreatic gland, in diseased liver, in molasses, &c., and is formed by the hydrolysis of many proteins or by their decay.

It has also been obtained synthetically, as indicated by the following series of reactions:



(Compare also B., 1899, 3638; Am. C. J., 1911, 368; J. C. S., 1914, 1152.)

Of the numerous **polyhydroxy-phenolic acids**, the following may be mentioned:

**Protocatechuic acid**, 3 : 4-*Dihydroxy-benzoic acid*, is obtained by fusing various resins, such as catechu, benzoïn, and kino, with alkali. It may be prepared synthetically, together with the 2 : 3-dihydroxy-acid, by heating catechol,  $C_6H_4(OH)_2$ , with ammonium carbonate. It crystallizes in glistening needles or plates, and is readily soluble in water; the solution is coloured green by ferric chloride, then—after the addition of a very little sodium carbonate—blue, and finally red. Like catechol it possesses reducing properties. Its mono-methyl ether is **vanillic acid**, or 4-*hydroxy-3-methoxy-benzoic acid*,  $C_6H_3(CO_2H)(O \cdot CH_3)(OH)$ , which is obtained by the oxidation of vanillin (Chap. XXV, D.) its dimethyl ether is the **veratric acid** of *sabadilla* seed (*Veratrum Sabadilla*), and its methylene ether is

**piperonylic acid**  $CH_2 \begin{array}{c} \diagup O \diagdown \\ \diagdown O \diagup \end{array} C_6H_3 \cdot CO_2H$ , which can be prepared,

among other methods, by the oxidation of piperic acid (this Chap., A5).

**Gallic acid**, 3 : 4 : 5-*Trihydroxy-benzoic acid*,  $C_6H_2(OH)_3CO_2H$ , occurs in nut-galls, in tea and many other plants, and as glucosides in several tannins. It is prepared by boiling tannin with dilute acids, or by allowing mould to form on its solution, and has also been obtained synthetically by various reactions. It crystallizes in fine silky needles ( $+H_2O$ ), dissolves readily in water, alcohol, and ether, and has a faintly acid and astringent taste. It evolves carbon dioxide readily when heated, yielding pyrogallol, reduces gold and silver salts, and yields a bluish-black precipitate with ferric chloride. Like pyrogallol, it is very readily oxidized in alkaline solution, with the production of a brown colour.

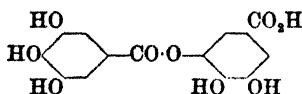
Gallic acid is used in the manufacture of blue-black inks. With ferrous sulphate it gives a pale-brown colour, which rapidly turns black on exposure to the air; the presence of a minute quantity of free sulphuric acid retards this oxidation, but when the acidified solution is used with ordinary paper the acid is neutralized by compounds present in the paper, and the oxidation takes place. Indigo carmine is added to the ink in order to give it a blue colour before oxidation occurs. *Dermatol* and *Airol* are bismuth derivatives (Chap. LXV, A2).

**Tannin** \* is the generic name given to the naturally occurring derivatives of polyhydroxy-benzoic acids which are used for converting skins into leather. One of the most important of these is **gallotannic acid**, present in nut-galls, sumach, &c., and is a derivative of pyrogallol or gallic acid; other tanning materials appear to contain derivatives of catechol, and are often termed phlobo-tannins in contradistinction to pyrogallol tannins. They are characterized by the readiness with which they yield a red precipitate of phlobaphene when their aqueous solutions are boiled with hydrochloric acid.

Some of the important tanning materials are: Oak bark, Wattle bark, from different species of *Acacia*, e.g. *A. arabica*, *dealbata*, *decurrans*, of Australia, South Africa, India; Myrabolan, the dried fruit of *Terminalia chebula* of India; Sumach (leaves of *Rhus coriaria*); Divi-divi, pod of *Caesalpinia coriaria* of South America; Cutch, extract of wood of *Acacia catechu* of India; Turwad, bark of twigs of *Cassia auriculata* of South India; Hemlock bark, Horse-chestnut bark, &c.

At one time tanners made their own infusions of extracts, but it has become customary to extract the material at central factories, to evaporate the aqueous extract in multiple-effect film-evaporators under reduced pressure, and to put on the market a solid extract containing very little insoluble matter and 50–60 per cent of tannins. The process of vegetable or bark tanning consists in converting the gelatin of the skin into an insoluble compound with tannin. The result is to give a durable, flexible product, which does not undergo putrefactive changes. Before tanning, the skin has to undergo several preliminary treatments, e.g. liming to remove hair, deliming with acid or with decomposing dung or bran, splitting into layers, &c.

Gallotannic acid, commonly termed tannic acid, is probably a glucoside in which the five OH groups of *d*-glucose are esterified by *m*-digallic acid:



(cf. Glycosides, Chap. LVI, F.). All tannins are amorphous solids readily soluble in water or alcohol, but practically

\* M. Nierenstim, *Natural Organic Tannins*, London, 1934.

insoluble in ether, and yield precipitates with alkaloids, gelatins, and the salts of many heavy metals.

**Quinic acid**, which is found in quinine bark, coffee beans, &c., is a tetrahydroxy-hexahydro-benzoic acid,  $C_6H_7(OH)_4CO_2H$ . It crystallizes in colourless prisms and is optically active, *Russel and Todd* (J. C. S., 1934 and 1937) have synthesized compounds having a flav-pinacol structure (cf. Chap. LXIV, B.) which are indistinguishable from natural phlobo-tannins.

#### 4. ALCOHOL- AND KETO-ACIDS

The monobasic aromatic alcohol-acids, which possess at one and the same time the characters of acids and of true alcohols (p. 505), contain the alcoholic hydroxyl in the side chain; this hydroxyl is consequently eliminated together with the side chain when the compound is oxidized.

In behaviour they approximate very closely to the hydroxy-acids of the fatty series, as the phenylated derivatives of which they thus appear; at the same time they yield, as phenyl derivatives, nitro-compounds, &c., although those compounds can often not be prepared directly, on account of the readiness with which the acids are oxidized. They differ from the phenolic acids in being more soluble in water, less stable, and non-volatile; as alcohols many of them give up water and yield unsaturated acids (which the phenolic acids can never do), and they can be esterified by hydrobromic acid, &c., with the formation of halide-substitution acids, &c.

The hydroxy acids may be either primary, secondary, or tertiary alcohols, e.g.  $OH\cdot CH_2\cdot C_6H_4\cdot COOH$ ,  $C_6H_5\cdot CH(OH)\cdot COOH$ , and  $C_6H_5\cdot CH_2\cdot C(CH_3)(OH)\cdot COOH$ . The tertiary can sometimes be prepared directly by the oxidation, by means of a permanganate, of acids containing a tertiary hydrogen atom ( $:CH$ ).

**Mandelic acid**, *Phenyl-glycollic acid*,  $C_6H_5\cdot CH(OH)\cdot CO_2H$  (1835), is formed by hydrolysing the glucoside amygdalin with hydrochloric acid, and synthetically by the hydrolysis of benzaldehyde-cyanhydrin, mandelonitrile,  $C_6H_5\cdot CH(OH)\cdot CN$ . It forms glistening crystals, dissolves somewhat readily in water, and melts at  $133^\circ$ .

Mandelic acid possesses an asymmetric carbon atom and exists in two optically active modifications, and these can form

a racemic compound (*para*-mandelic acid) in the same manner as *d*- and *l*-tartaric acids.

The acid obtained synthetically is the racemic acid, but this can be resolved (1) by the aid of chinchonine when the chinchonine salt of the *d*-acid crystallizes first; (2) by means of green mould, *penicillium glaucum*, which when grown on a solution of the ammonium salt of the acid destroys the *laevo* modification; (3) by partially esterifying the racemic acid with an optically active alcohol, e.g. *l*-menthol; the non-esterified acid is then *l*-rotatory, as the *d*-acid is somewhat more readily esterified by *l*-menthol than the *l*-acid (cf. Chap. L, A.). The acid obtained from amygdalin is the *laevo* compound. It is comparable with lactic acid,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$ , yielding, like the latter, formic acid (together with benzoic) when oxidized; hydriodic acid reduces it to phenyl-acetic acid, just as it does lactic acid to propionic.

***o*-Hydroxymethyl-benzoic acid**,  $\text{OH}\cdot\text{CH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{OH}$ , which is isomeric with mandelic acid, is unstable in the free state; as an ortho-compound, it readily yields the anhydride or

lactone, **Phthalide**,  $\text{C}_6\text{H}_4\begin{matrix} \text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CO} \end{matrix} \text{O}$ , which is obtained by the

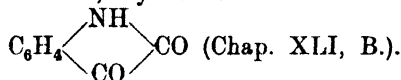
reduction of phthalic anhydride or chloride. It crystallizes in needles or plates, and can be sublimed unaltered.

**Tropic acid**,  *$\alpha$ -Phenyl- $\beta$ -hydroxy-propionic acid*,  $\text{OH}\cdot\text{CH}_2\cdot\text{CHPh}\cdot\text{CO}_2\text{H}$  (fine prisms), is obtained together with tropine by boiling atropine with baryta water; it is reconverted into atropine when warmed with tropine and hydrochloric acid. It exists in *d*-, *l*-, and *r*-modifications. Tropic acid can be synthesized from ethyl phenyl-acetate and ethyl formate, which react in the presence of sodium (*Claisen* reaction), yielding ethyl formylphenylacetate,  $\text{CHO}\cdot\text{CHPh}\cdot\text{CO}_2\text{Et}$ , or the enolic form,  $\text{OH}\cdot\text{CH}:\text{CPh}\cdot\text{CO}_2\text{Et}$ , which is reduced in ethereal solution by means of aluminium amalgam to ethyl tropate (*Müller*, B., 1918, 252).

**Benzoyl-formic acid**, *Phenyl-glyoxylic acid*,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CO}_2\text{H}$ , is obtained synthetically by the hydrolysis of benzoyl cyanide,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CN}$ , with cold fuming  $\text{HCl}$  (*Claisen*, 1877), and also by the cautious oxidation of mandelic acid or acetophenone. It is an oil which only solidifies slowly, and when distilled is largely decomposed into carbon monoxide and benzoic acid. It reacts similarly to isatin with benzene containing thiophene

and sulphuric acid, and shows the normal reactions of the ketonic acids with  $\text{NaHSO}_3$ ,  $\text{HCN}$ ,  $\text{NH}_2\cdot\text{OH}$ , &c.

***o*-Nitro-benzoyl-formic acid**,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{CO}_2\cdot\text{H}$ , which can be prepared from *o*-nitro-benzoyl cyanide, yields ***o*-amino-benzoyl-formic acid**, ***isatic acid***,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{CO}_2\text{H}$  (a white powder), upon reduction; when a solution of the latter is warmed, it yields its intramolecular anhydride (lactam), **isatin**,



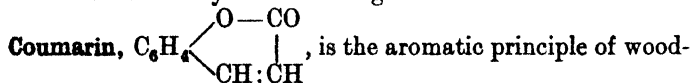
**Benzoyl-acetic acid**,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  (*Baeyer*), is the analogue of acetoacetic acid, and, like the latter, can be used for numerous syntheses. It is obtained as its ethyl ester (which is soluble in cold sodium hydroxide solution) by dissolving ethyl phenyl-propiolate in concentrated sulphuric acid and pouring the solution into water; or, better, by the action of sodium ethoxide upon a mixture of ethyl benzoate and acetate (*Claisen's* condensation, Chap. IX, H.). It is crystalline, melts at  $103^\circ$ , and readily splits up into carbon dioxide and acetophenone,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3$ ; the aqueous solution is coloured a beautiful violet by ferric chloride.

Aryl ketonic acids when heated with aniline lose  $\text{CO}_2$  and  $\text{H}_2\text{O}$  yielding azo-methines from which aldehydes and aniline are readily formed by hydrolysis (*Bouveault*):



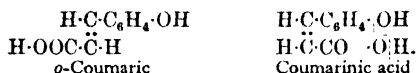
## 5. UNSATURATED MONOBASIC PHENOLIC ACIDS

**Hydroxy-cinnamic or Coumaric Acids**,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ .—The ortho-acid is present in melilot (*Melilotus officinalis*), and can be prepared by diazotizing *o*-amino-cinnamic acid, or from salicylic aldehyde by *Perkin's* synthesis. The alcoholic solution is yellow with a green fluorescence.



ruff (*Asperula odorata*), and is also found in the Tonquin bean and other plants. It is obtained by the elimination of water from *o*-coumaric acid by means of acetic anhydride. It crystallizes in prisms, dissolves readily in alcohol, ether, and hot water; melts at  $67^\circ$ , and boils at  $290^\circ$ . It dissolves in sodium

hydroxide solution, yielding the sodium salt of **coumarinic acid**. This salt is stereo-isomeric with that of *o*-coumaric acid. The free acid itself appears to be incapable of existence, as it is immediately converted into coumarin (its anhydride), but various derivatives are known. *o*-Coumarinic acid is regarded as the *cis*-compound, as it yields an anhydride (cf. Maleic Acid, Chap. X, B.). The stereo-isomeric *o*-coumaric acid is the *trans*-acid (cf. Fumaric Acid):



Synthetic coumarin is used in place of Tonquin bean and is very useful for fixing other odours. It can be synthesized by Perkin's synthesis (p. 511) from salicylaldehyde, or from *o*-chloro-benzal chloride,  $\text{Cl} \cdot \text{C}_6\text{H}_4 \cdot \text{CHCl}_2$ . This latter condenses with acetic acid in the presence of potassium acetate, yielding *o*-chloro-cinnamic acid, which is readily reduced to *o*-chloro-phenylpropionic acid,  $\text{Cl} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$ , from which the corresponding *o*-hydroxy acid is obtained by heating with alkali. The free hydroxy acid loses water when

heated, yielding **hydro-coumarin**,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{O} \cdot \text{CO} \diagdown \\ \text{CH}_2 \cdot \text{CH}_2 \end{array}$ , from

which coumarin is formed by the action of bromine vapour at  $270^\circ$ – $300^\circ$  (M., 1913, 1665).

The usual method of synthesis is from *o*-cresol and phosgene. These yield dicresyl carbonate  $(\text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{O})_2\text{CO}$  the tetrachloro derivative of which  $(\text{CHCl}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{O})_2\text{CO}$  with acetic anhydride and sodium acetate (*Perkin* synthesis) and subsequent distillation yields coumarin (*Raschig*).

Coumarin (*cis*-anhydride) can be converted into coumaric (trans acid) by the following reactions. The anhydride when warmed with 20 per cent sodium bisulphite solution yields

**hydro-coumarin sulphonate**,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{O} - \text{CO} \diagdown \\ \text{CH}_2 \cdot \text{CH} \cdot \text{SO}_3\text{Na} \end{array}$ , which

is converted into sodium hydro-coumaric sulphonate,

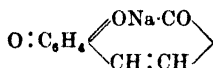


when warmed with alkali. The latter compound readily yields coumaric acid when hydrolysed (*Dodge*, J. A. C. S., 1916, 446).

*Jordan and Thorpe* (J. C. S., 1915, 396) suggest that the sodium salt of coumarinic acid, which is yellow, has the ortho-quinonoid structure,  $O:C_6H_4:CH:CH_2 \cdot CO_2Na$ , whereas the acid has the normal benzene structure



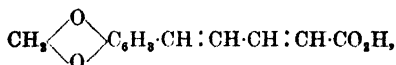
and *Dey* (*ibid.* 1622) suggests that the yellow salts of hydroxy-coumarin also have quinone structures with quadrivalent oxygen.



Coumarin derivatives can be synthesized by the condensation of ketonic esters such as ethyl aceto-acetate, ethyl benzoyl-acetate, and ethyl acetone-dicarboxylate with phenols or naphthols in the presence of sulphuric acid (*Pechmann*, B., 1884, 929, 1646, 2187; 1899, 3681; 1901, 423; *Dey*, loc. cit.).

**3 : 4-Dihydroxy-cinnamic acid**, *Caffeic acid*,  $(OH)_2 \cdot C_6H_3 \cdot CH:CH \cdot CO_2H$ , crystallizes in yellow prisms, and is obtained from caffetannic acid, whose mono-methyl ether is **ferulic acid** (from asafoetida); the isomeric **umbellic acid** or *p*-hydroxy-*o*-coumaric acid readily changes into the anhydride corresponding to coumarin, viz. **umbelliferone**,  $C_9H_6O_3$ ; this last-named compound is present in varieties of *Daphne*.

Related to the above is **piperic acid**:



a decomposition product of piperine (p. 688), which crystallizes in long needles.

## B. Dibasic Acids

The saturated dibasic acids of the aromatic are analogous to those of the aliphatic series, i.e. the acids of the oxalic series (Chap. X, A.). As dibasic acids they can yield normal and acid salts, normal and acid esters, amides and amic acids, anilides and anilic acids, &c.

Both carboxyl groups may be attached to carbon atoms of the nucleus, or both to carbon atoms of side chains; or one attached to the nucleus and one to a side chain, e.g.

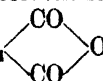


$\text{CO}_2\text{H}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3\cdot\text{CO}_2\text{H}$ . When the two carboxyl groups are attached to the nucleus in ortho-positions, an inner anhydride of the type of succinic anhydride (p. 267) is readily formed. The isomeric meta- and para-dibasic acids do not yield such anhydrides.

Substituted dibasic acids are also known, e.g. hydroxy-, nitro- and amino-dibasic acids.

1. **Phthalic acid**, *Benzene-o-dicarboxylic acid*,  $\text{C}_6\text{H}_4(\text{CO}_2\text{H})_2$  (*Laurent*, 1836), is formed when any *o*-di-derivative of benzene, which contains two carbon side chains, is oxidized by  $\text{HNO}_3$  or  $\text{KMnO}_4$ , but not by  $\text{CrO}_3$  (cf. p. 507); it can be formed by the oxidation of naphthalene by nitric acid or of naphthalene tetrachloride, and also of anthracene derivatives. At the present time phthalic acid is prepared on the commercial scale by oxidizing naphthalene with concentrated sulphuric acid in the presence of a small amount of mercury or mercuric sulphate at  $220^\circ$ – $300^\circ$ . It crystallizes in short prisms or plates, melts at  $213^\circ$ , and is readily soluble in water, alcohol, and ether. When heated above its melting-point, it yields the anhydride. When heated with lime, it yields benzoic acid or benzene according to the relative amounts of acid and lime used. Chromic acid disintegrates it completely, while sodium amalgam converts it into dihydro-, tetrahydro-, and finally hexahydro-phthalic acid (see below). Its barium salt,  $\text{C}_6\text{H}_4(\text{CO}_2)_2\text{Ba}$ , is sparingly soluble in water.  $K_1 \times 10^4 = 12.0$  and  $K_2 \times 10^4 = 0.40$ .

The acid ester  $\text{CO}_2\text{H}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{Et}$  is formed from the anhydride and alcohol and on esterification yields the normal ester,  $\text{C}_6\text{H}_4(\text{CO}_2\text{Et})_2$  which is used as a denaturant for alcohol. The cyclohexyl ester is used as a solvent for cellulose esters.

**Phthalic anhydride**,  $\text{C}_6\text{H}_4$  O, crystallizes in long

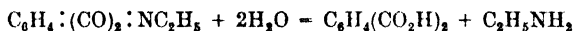
prisms which can be sublimed; it melts at  $131.6^\circ$ , boils at  $284^\circ$ , and is a very valuable synthetic reagent used in the manufacture of phthalic esters, phthalimide, anthranilic acid (p. 519), anthraquinone (Chap. XXXII, A.), phenolphthalein and eosin dyes (Chap. XXX), and glyptal plastics (Chap. LX, C.).

It is manufactured on a large scale by oxidizing naphthalene with fuming sulphuric acid (20 per cent oleum) at  $285^\circ$ – $295^\circ$  with a little  $\text{HgSO}_4$  and  $\text{CuSO}_4$  as catalyst, or still better by oxidizing naphthalene in the vapour phase with atmospheric

oxygen using vanadium pentoxide as catalyst. Yield 90 per cent.

**Phthalimide**,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CO} \\ \diagdown \text{CO} \end{array} \text{NH}$ , corresponds with succinimide

in many respects. It is obtained by passing dry ammonia over heated phthalic anhydride, and readily gives rise to metallic derivatives. The *potassium salt*  $\text{C}_6\text{H}_4(\text{CO})_2\text{NK}$ , obtained by the action of aqueous caustic potash on an alcoholic solution of the imide, readily reacts with alkyl iodides, yielding alkylated phthalimides, e.g.  $\text{C}_6\text{H}_4(\text{CO})_2\text{NC}_2\text{H}_5$ , and when these are hydrolysed, primary amines, free from secondary and tertiary, are obtained, e.g.:



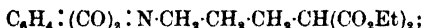
(*Gabriel*, B., 1887-1897). Numerous primary amines, including halogenated bases, which are difficult to prepare by other methods, have been obtained in this way. *E. Fischer* (B., 1901, 455) has also used the same method for the preparation of the complex amine ornithine,



$\alpha\delta$ -diamino-*n*-valeric acid. The various steps are: Potassium phthalimide and trimethylene bromide yield



and this on condensation with ethyl sodio-malonate gives



and on bromination and subsequent hydrolysis and loss of carbon dioxide  $\text{C}_6\text{H}_4 : (\text{CO})_2 : \text{N} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHBr} \cdot \text{CO}_2\text{H}$  is obtained. Aqueous ammonia converts this into the corresponding amino-compound, and subsequent hydrolysis gives ornithine.

Ethylene and propylene oxides react with potassium phthalimide yielding compounds of the type  $\text{C}_6\text{H}_4(\text{C}_2\text{O}_2) \cdot \text{N} \cdot \text{CH}_2 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_3$ , and this on hydrolysis gives  $\beta$ -hydroxy-*n*-propylamine,  $\text{CH}_3 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_2 \cdot \text{NH}_2$  (*Gabriel*, B., 1917, 819).

The chloride, **phthalyl chloride**, which is obtained by the action of  $\text{PCl}_5$  upon the acid or the anhydride, appears to have the normal constitution  $\text{C}_6\text{H}_4(\text{COCl})_2$ , as it yields the compound  $\text{C}_6\text{H}_4[\text{CO} \cdot \text{CH}(\text{CO}_2\text{Et})_2]_2$  with ethyl sodio-malonate

(Scheiber, A., 1912, **389**, 211; B., 1912, 2252). When heated with  $\text{AlCl}_3$  it gives an isomeride which probably has the unsym-

metrical formula  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CCl}_2 \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{O}$ , as with benzene and  $\text{AlCl}_3$

it yields phthalophenone,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CPh}_2 \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{O}$ . The symmetrical

structure for the original compound is supported by a study of its reaction with aniline, and also by the value for its molecular volume (Ost, A., 1912, **392**, 245). For physico-chemical study of the two forms, cf. Csanyi, M., 1919, 81; Ott and Pfeiffer, B., 1922, 413.

2. **Isophthalic acid** (1 : 3), prepared from *m*-xylene, crystallizes in slender needles from hot water, in which it is only sparingly soluble; it sublimes without forming an anhydride. The barium salt is readily soluble in water.  $K \times 10^4 = 2.9$ .

**Uvic acid** is 5-methyl-isophthalic acid, and may be obtained by oxidizing mesitylene.

3. **Terephthalic acid** (1 : 4) is obtained by the oxidation of *p*-xylene, cymene, &c., and especially of oil of turpentine or oil of cumen. It forms a powder almost insoluble in alcohol and water, and sublimes unchanged. For its preparation *p*-toluic acid is oxidized by potassium permanganate. The barium salt is only sparingly soluble.

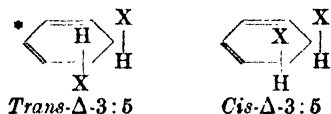
A. Baeyer's researches have introduced a whole series of reduction products of phthalic acid, generally known as hydro-phthalic acids. The isomers among them differ from one another either by the position of the double bond in the ring (*structural isomerism*), or by the spatial arrangement of the carboxyl groups with respect to the ring (*stereo-isomerism*). This latter type is attributable to the fact that in the true aromatic acids the hydrogen and substituents are coplanar with the carbon ring, but on reduction, the formula becomes multiplanar and isomerism of the type met with in the cyclopropane derivatives becomes possible (Chap. XVI), viz. *cis* and *trans* forms.

Of the **hydro-phthalic acids** (A., **269**, 147) there are now known: Five *dihydro-acids* (two of which are stereo-isomeric), four *tetrahydro-acids* (of which two again are stereo-isomeric), and two *hexahydro-acids* (which are stereo-isomers). Of the **hydro-terephthalic acids** (A., **258**, 1), five *dihydro*-, three *tetra*-

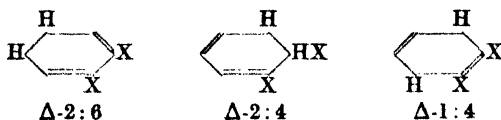
*hydro*-, and two *hexahydro*-acids are known, two in each group being stereo-isomeric.

The following principles have largely served for determining the position of the double bonds in these compounds: (1) When bromine substitutes in a carboxylic acid it takes up the  $\alpha$ -position to the carboxyl (i.e. it is attached in the benzene nucleus to the same carbon atom to which the carboxyl is linked). (2) If two bromine atoms stand in the *ortho*-position to one another in a reduced benzene nucleus, they are eliminated, without replacement, by the action of zinc dust and glacial acetic acid; whereas, if they stand in the *para*-position, they are replaced by hydrogen. (3) As in the case of the aliphatic unsaturated acids, boiling with sodium hydroxide solution often gives rise to an isomeric acid, due to the "wandering" of a double bond in the direction of a carboxyl group (p. 187). (4) The stereo-isomeric modifications are easily transformed one into the other.

The relations existing between the five known dihydro-phthalic acids may be taken as an example. When phthalic acid is reduced by sodium amalgam in presence of acetic acid, *trans*- $\Delta$ -3:5-dihydro-phthalic acid is produced, and this changes into the *cis*- $\Delta$ -3:5-acid when heated with acetic anhydride:



Both of these yield the  $\Delta$ -2:6-dihydro-acid when warmed with alkali. When the dihydrobromide of the latter acid is treated with alcoholic potash, the  $\Delta$ -2:4-dihydro-acid results, and, lastly, the anhydride of this yields the anhydride of the  $\Delta$ -1:4-dihydro-acid when heated:



\* In these formulæ  $X = CO_2H$ ,  $\Delta$  denotes the double bond, and the numbers refer to the carbon atoms at which the double bonds start.  $\Delta$ -3:5 indicates two double bonds, one between carbons 3 and 4, and a second between carbons 5 and 6.

All the dihydro-phthalic acids give anhydrides with the exception of the *trans*- $\Delta$ -3:5-acid, which in this respect resembles fumaric acid.

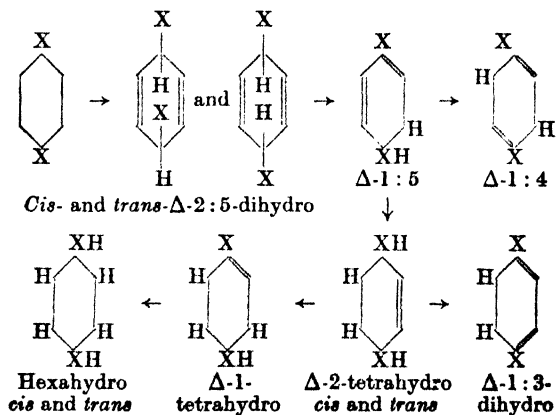
The following relationships have been established between the hydro-terephthalic acids:

Terephthalic acid reduced with pure sodium amalgam in faintly alkaline solution gives a mixture of *cis*- and *trans*- $\Delta$ -2:5-dihydro-acids, both of which on oxidation readily yield terephthalic acid. When boiled with water both are converted into the  $\Delta$ -1:5-dihydro-acid, and when boiled with caustic soda solution into the  $\Delta$ -1:4-dihydro-acid. This acid is the most stable of the dihydro-acids, and is always obtained by the reduction of terephthalic acid unless great care is taken.

When reduced with sodium amalgam the  $\Delta$ -1:5-acid is converted into a mixture of *cis*- and *trans*- $\Delta$ -2-tetrahydro-acids, which are also formed when the original acid is reduced with pure sodium amalgam (B., 1928, 871). Both acids readily combine with bromine, which can again be removed by means of zinc dust; this dibromide, when warmed with alcoholic potash, gives the  $\Delta$ -1:3-dihydro-acid, which cannot be obtained directly by the reduction of terephthalic acid.

The  $\Delta$ -1-tetrahydro-acid may be obtained by warming the  $\Delta$ -2-acid with sodium hydroxide solution.

The  $\Delta$ -1-acid yields a mixture of two stereo-isomeric dibromides (*cis* and *trans*), and these when reduced with zinc dust and acetic acid yield the *cis*- and *trans*-hexahydro-terephthalic acid:



The completely hydrogenated acids show great differences from the partially hydrogenated. Thus, hexahydro-terephthalic acid is exactly similar to a saturated acid of the fatty series, cold permanganate of potash has no effect upon it, while bromine substitutes (upon warming).

On the other hand, the partially hydrogenated acids closely resemble the unsaturated acids of the fatty series. They are very readily oxidized by cold permanganate, and take up bromine or hydrobromic acid until the saturation stage of the hexa-methylene ring is reached. All of the hydro-acids can be transformed back into phthalic acid (A., 1894, 280, 94).

For **hydro-isophthalic acids** see *W. H. Perkin, Jun.*, and *S. S. Pickles, P.*, 1905, 75, and *Baeyer and Villiger, A.*, 1893, 276, 255.

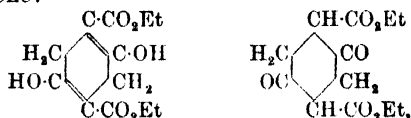
A large number of substitution products of the phthalic acids are known, e.g. **chloro-** and **bromo-phthalic acids** (which are used in the eosin industry), **nitro-**, **amino-**, **hydroxy-** and **sulphophthalic acids**, &c.

## HYDROXY-PHTHALIC ACIDS

**2:5-Dihydroxy-terephthalic acid**, *quinol-p-dicarboxylic acid*,  $C_6H_2(OH)_2(CO_2H)_2$ , in which both the hydroxyls and the carboxyls are respectively in the *p*-position to one another, is obtained as its ethyl ester by the action of bromine upon succinylo-succinic ester, or of sodium ethoxide upon dibromo-acetoacetic ester. The free acid breaks up into quinol and carbon dioxide when distilled, and is converted by nascent hydrogen into succinylo-succinic acid.

**Succinylo-succinic acid**, **2:5-dihydroxy- $\Delta^{1:4}$ -dihydro-terephthalic acid**,  $C_6H_4(OH)_2(CO_2H)_2$ , is obtained as its ethyl ester by the action of sodium upon ethyl succinate (see p. 403). The **ethyl ester** crystallizes in triclinic prisms which melt at  $126^\circ$ , and dissolves in alcohol to a bright-blue fluorescent liquid which is coloured cherry-red by ferric chloride. It contains two replaceable hydrogen atoms, being analogous to acetoacetic ester. The free acid, on losing carbon dioxide, changes into tetrahydro-quinone or *p-diketo-hexamethylene*.

The ester may be represented as a dihydroxylic compound or as a diketone:



and reacts as a tautomeric substance (cf. Ethyl Acetoacetate).

### C. Polybasic Acids

Benzene *s*-tricarboxylic acid or **trimesic acid**,  $\text{C}_6\text{H}_3(\text{COOH})_3$ , can be obtained by the oxidation of mesitylene. The isomeric unsym. acid or **trimellitic acid** is obtained by the oxidation of colophonium, and the adjacent acid or **hemimellitic acid** is obtained by oxidizing naphthalene-1 : 8-dicarboxylic acid.

The benzene tetracarboxylic acids,  $\text{C}_6\text{H}_2(\text{CO}_2\text{H})_4$ , **prehnitic acid** [1 : 2 : 3 : 4], **mellophanic acid** [1 : 2 : 3 : 5], and **pyromellitic acid** [1 : 2 : 4 : 5], are obtained by heating mellitic acid or its hexahydro-derivatives.

**Mellitic acid**,  $\text{C}_6(\text{CO}_2\text{H})_6$ , occurs in peat as aluminium salt or honey-stone,  $\text{C}_{12}\text{Al}_2\text{O}_{13} + 18\text{H}_2\text{O}$ , which crystallizes in octahedra, and is also formed by the oxidation of lignite or graphite with  $\text{KMnO}_4$ . It forms fine silky needles of great stability, can neither be chlorinated, nitrated, nor sulphonated, but is readily reduced by sodium amalgam to **hydromellitic acid**,  $\text{C}_6\text{H}_6(\text{CO}_2\text{H})_6$ , and yields benzene when distilled with lime.

As regards the esterification of these polybasic acids, it has been found that carboxylic groups which have other carboxylic groups in two ortho-positions cannot be esterified by the usual catalytic process, e.g. on esterification by the *Fischer-Speyer* method, hemimellitic acid and prehnitic acid yield dimethyl esters only, pyromellitic acid yields a tetramethyl ester, and mellitic acid is not acted on (*V. Meyer and Sudborough, B.*, 1894, 3146).

## XXVII. AROMATIC COMPOUNDS CONTAINING TWO OR MORE BENZENE NUCLEI. DIPHENYL GROUP

The aromatic compounds hitherto considered, with the exception of azobenzene, benzophenone, &c., contain but one benzene nucleus. In addition to these, however, a considerable number of compounds are known which contain two or more such nuclei united in a variety of ways. Such compounds are usually arranged in the following groups:

1. **Diphenyl group**; this comprises the compounds with two benzene nuclei directly united. The parent substance of the group is diphenyl,  $C_6H_5 \cdot C_6H_5$ .

2. **Diphenyl-methane group**; this includes all compounds with two benzene nuclei attached to a single carbon atom. The parent substance is diphenyl-methane,  $C_6H_5 \cdot CH_2 \cdot C_6H_5$ .

3. **Dibenzyl or stilbene group**, which comprises compounds containing two benzene nuclei linked together by a chain of two or more carbon atoms, e.g. dibenzyl,  $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot C_6H_5$ , and stilbene,  $C_6H_5 \cdot CH : CH \cdot C_6H_5$ .

4. **Triphenyl-methane group**, which contains the compounds with three benzene nuclei attached to a single carbon atom, e.g. triphenyl-methane,  $CH(C_6H_5)_3$ .

5. **Compounds with condensed benzene nuclei**, i.e. compounds with two or more nuclei with each pair of rings having a pair of carbon atoms in common (see Naphthalene and Anthracene).

### DIPHENYL GROUP

**Diphenyl** is related to benzene in much the same manner as ethane to methane:



Its molecule consists of two benzene nuclei directly united. Its method of synthesis by *Fittig*, by the action of sodium on an ethereal solution of monoiodo-benzene, or of copper-bronze at  $230^\circ$  (*Ullmann*, A., 1904, **332**, 38) is analogous to the formation of ethane by the action of zinc or sodium on methyl iodide:

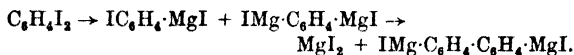




An interesting synthesis is from phenyl magnesium bromide and anhydrous  $\text{CrCl}_3$  or  $\text{CuCl}_2$ ; in both cases the metallic chloride is reduced to the lower 'ous form (J. C. S., 1914, 1057; 1919, 559):



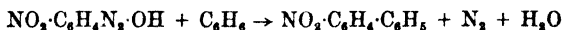
Another synthesis is from *p*-di-iodo-benzene and magnesium. The mono- and di-magnesium compounds are first formed, and these react, yielding  $\text{IMg}\cdot\text{C}_6\text{H}_4\cdot\text{C}_6\text{H}_4\cdot\text{MgI}$ , which is converted into diphenyl by the action of water (B., 1914, 1219):



It is also formed by passing the vapour of benzene through a red-hot tube. It is contained in coal-tar, crystallizes in large colourless plates, melts at  $71^\circ$ , boils at  $254^\circ$ , and is readily soluble in alcohol and ether.

Diphenyl derivatives are usually formed as by-products in *Sandmeyer's* method for preparation of halide derivatives from diazonium compounds (Chap. XXII, A.), particularly when nitro-groups are present (*Ullmann*, B., 1901, 3802; 1905, 725), or when a diazonium salt is warmed with EtOH and zinc dust, Cu or Fe powders.

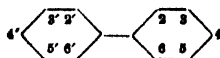
They are also formed by the action of a diazohydroxide on benzene:



(*Gomberg* and others, J. A. C. S., 1924, 2339; 1926, 1372; *Grieve* and *Hay*, J. C. S., 1934, 1797).

Chromic acid oxidizes diphenyl to benzoic acid, one of the two benzene nuclei being destroyed. From this and from its synthesis, the formula of diphenyl must be  $\text{C}_6\text{H}_5\cdot\text{C}_6\text{H}_5$ .

**Derivatives** (*Schultz*, A., 207, 311).—Like benzene, diphenyl is the mother substance of a series of derivatives which closely resemble the corresponding benzene derivatives. With poly-substituted derivatives the substituents are usually denoted by the following numbers, according to the position occupied:



Mono-substituted derivatives exist in *o*-, *m*-, or *p*-forms, according to the position of the substituent with reference to

the point of union of the two nuclei. The number of di-substituted derivatives is still larger. The constitution of these is elucidated from their syntheses, from their products of oxidation, or by conversion into compounds of known constitution; thus a chloro-diphenyl,  $C_{12}H_9Cl$ , which yields *p*-chloro-benzoic acid when oxidized by chromic acid, is obviously *p*-chloro-diphenyl. Whether all the substituents are attached to the one nucleus or are distributed between the two, can also be proved by an examination of the products of oxidation.

Substituents usually take up the *p*-position; in di-derivatives the *p-p*- (and to a lesser extent the *o-p*-) position.

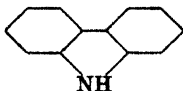
The spatial arrangement of the diphenyl molecule has attracted attention (cf. Chap. L, A5).

**Di-*p*-diamino-diphenyl**, *benzidine*,  $NH_2 \cdot C_6H_4 \cdot C_6H_4 \cdot NH_2$  (Zinin, 1845), is obtained by the reduction of *p-p*-dinitro-diphenyl (the direct nitration product of diphenyl); also, together with diphenylene, by the action of acids upon hydrazobenzene, the latter undergoing a molecular transformation (Chap. XXII, C2.):  $C_6H_5 \cdot NH \cdot NH \cdot C_6H_5 \rightarrow NH_2 \cdot C_6H_4 \cdot C_6H_4 \cdot NH_2$ ; it is consequently formed directly from azobenzene by treating it with tin and hydrochloric acid.

Benzidine is a diacid base which crystallizes in colourless silky plates, is readily soluble in hot water or alcohol, and melts at  $122^\circ$ . Its **sulphate**,  $C_{12}H_{10}(NH_2)_2 \cdot SO_4H_2$ , is sparingly soluble. Like its homologues (tolidine, &c.), it is of special importance in the colour industry, as its diazonium-compound couples with naphthol-sulphonic or naphthylamine-sulphonic acids, yielding the "substantive" or direct cotton dyes (cf. Chap. LIX, B2).

The isomeric **diphenylene**, 2:4'-diamino-diphenyl, may be obtained from 2:4'-dinitro-diphenyl, and also as a by-product in the preparation of benzidine from azobenzene. It crystallizes in needles, melting at  $45^\circ$ , and yields a sulphate which is readily soluble.

### Carbazole,



the imide of diphenyl, is contained in coal-tar and in crude anthracene. It is separated from the hydrocarbons by treatment with solid potash, when the  $>N \cdot K$  compound is formed,

and subsequently decomposed by water. It is formed by distilling *o*-amino-diphenyl over lime at a low red heat, or by passing the vapour of diphenyl-amine through red-hot tubes, just as diphenyl is obtained from benzene,  $(C_6H_5)_2NH = (C_6H_4)_2NH + H_2$ .

A good yield is obtained by heating 2 : 2-diaminodiphenyl with 25 per cent sulphuric acid at  $200^\circ$  (Blank, B., 1891, 306). Tetrahydrocarbazole (one reduced benzene ring) is obtained by boiling cyclohexanone-phenylhydrazone with hydrochloric acid and on dehydrogenation yields carbazole.

It crystallizes in colourless plates sparingly soluble in cold alcohol, melts at  $245^\circ$ , distils unchanged, and is characterized by the readiness with which it sublimes. Concentrated sulphuric acid dissolves it to a yellow solution, and it forms an acetyl- and a nitro-compound, &c. The nitrogen in it occupies the di-ortho-position; it thus appears, like indole, to be a pyrrole derivative, and it shows, in fact, most striking analogies to the latter.

**Benzidine-mono-, di-, &c., sulphonic acids**, e.g.  $C_{12}H_8(NH_2)_2(SO_3H)_2$ , are of technical importance. The **dihydroxy-diphenyls**,  $C_{12}H_8(OH)_2$ , of which four isomers are known, are formed (a) by diazotizing benzidine, (b) by fusing diphenyl-disulphonic acid with potash, and (c) by fusing phenol with potash or by oxidizing it with permanganate; in the last case hydrogen is separated and two benzene residues join together.

**Diphenylene oxide**,  $\begin{array}{c} C_6H_4 \\ | \\ C_6H_4 \end{array} \rangle O$ , is obtained by distilling phenol

with plumbous oxide; it crystallizes in plates which distil without decomposition.

The **carboxylic acids** of diphenyl are obtained (1) from the corresponding nitriles, prepared by distilling the sulphonic acids of diphenyl with KCN, e.g. **di-*p*-diphenyl-dicarboxylic acid**,  $C_{12}H_8(CO_2H)_2$ , a white powder insoluble in water, alcohol, and ether; (2) by the oxidation of phenanthrene and similar compounds, e.g. **diphenic acid**,  $CO_2H \cdot C_6H_4 \cdot C_6H_4 \cdot CO_2H$ , the 2 : 2'-dicarboxylic acid, crystallizing in needles or plates which are readily soluble in the solvents just mentioned; m.-pt.  $229^\circ$ . Both of these are dibasic acids, which yield diphenyl when heated with soda-lime.

The homologues of diphenyl are, like the latter, obtained by means of *Ullmann's* reaction. Analogous to benzidine is

*o*-tolidine,  $C_{12}H_6(CH_3)_2(NH_2)_2$ , m.-pt.  $128^\circ$ , similarly **di-anisidine**, **dimethoxy-benzidine**,  $C_{12}H_6(O\cdot CH_3)_2(NH_2)_2$ . All these compounds yield diazonium salts, which couple with naphthols and then sulphonic acids to form substantive dyes (Chap. LIX, B2).

Diphenyl may be regarded as monophenyl-benzene; the corresponding di- and triphenyl-benzenes are also known.

***p*-Diphenyl-benzene**,  $C_6H_4(C_6H_5)_2$ , may be obtained by the action of sodium upon a mixture of *p*-dibromo-benzene and bromo-benzene. It crystallizes in flat prisms, melts at  $205^\circ$ , and on oxidation yields diphenyl-monocarboxylic and terephthalic acids.

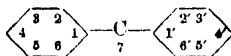
When hydrochloric acid gas is led into acetophenone,  $C_6H_5\cdot CO\cdot CH_3$ , a reaction analogous to the formation of mesitylene from acetone (p. 402) ensues, and ***s*-triphenyl-benzene**,  $C_6H_3(C_6H_5)_3$  (rhombic plates), is formed.

## XXVIII. DIPHENYL-METHANE GROUP

**Diphenyl-methane**,  $C_6H_5\cdot CH_2\cdot C_6H_5$ , is derived from methane by the replacement of two hydrogen atoms by two phenyl groups, and is thus closely related to phenyl-methane or toluene,  $C_6H_5\cdot CH_3$ . One important difference is that when oxidized it cannot yield an acid containing the same number of carbon atoms since it does not contain a methyl group. It can be oxidized to the secondary alcohol benzhydrol,  $(C_6H_5)_2CH\cdot OH$ , or the ketone benzophenone,  $(C_6H_5)_2CO$ . Compounds like diphenyl-ethane,  $(C_6H_5)_2CH\cdot CH_3$ , can yield acids.

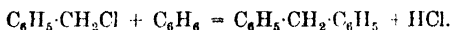
The various derivatives are obtained by substituting one or more of the twelve hydrogen atoms present in the diphenyl-methane molecule. If the substituent replaces any of the ten hydrogens directly attached to the benzene nuclei, a compound is formed which closely resembles the corresponding derivatives of benzene, e.g.  $C_6H_5\cdot CH_2\cdot C_6H_4\cdot NH_2$  closely resembles aniline. If, on the other hand, the substituent replaces a hydrogen atom of the methylene group, a compound with aliphatic properties is obtained, e.g.  $(C_6H_5)_2CH\cdot OH$  closely resembles a secondary aliphatic alcohol.

The method of numbering the carbon atoms in the diphenyl-methane molecule is usually as follows:



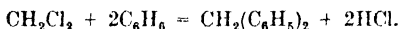
*Formation of diphenyl-methane and its derivatives.*

1. Diphenyl-methane is produced by the action of benzyl chloride upon benzene, in presence of zinc dust (*Zincke, A., 159, 374*), or of aluminium chloride (*Friedel and Crafts*):

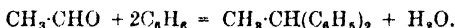


The homologues of benzene, and also the phenols and tertiary amines, may be used instead of benzene itself.

In an exactly analogous manner diphenyl-methane is obtained by the action of methylene chloride,  $\text{CH}_2\text{Cl}_2$ , upon benzene in presence of aluminium chloride:



2. Diphenyl-methane hydrocarbons are formed by the action of the aliphatic aldehydes, e.g. acetaldehyde or formaldehyde, upon benzene, &c., in the presence of concentrated sulphuric acid (*Baeyer, B., 1873, 963*). With formaldehyde diphenyl-methane, or with acetaldehyde diphenyl-ethane, is formed:



The acetaldehyde and formaldehyde are employed here in the form of paraldehyde and methylal. Formaldehyde itself condenses with aniline to diamino-, and with dimethyl-aniline to tetramethyl-diamino-diphenyl-methane. When aromatic aldehydes are used, triphenyl-methane derivatives are formed (*Chap. XXX*).

3. Aromatic alcohols react with benzene and sulphuric acid in an analogous manner (*V. Meyer*):



Similar reactions have also been brought about by means of ketones, aldehydo-acids, and keto-acids on the one hand, and phenol and dialkylated anilines on the other.

Benzophenone may be regarded as a diphenyl-methane derivative (see p. 496).

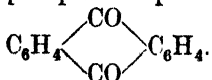
**Diphenyl-methane**,  $(C_6H_5)_2CH_2$ , is most conveniently prepared from benzyl chloride, benzene, and aluminium chloride. It crystallizes in colourless needles of very low melting-point ( $27^\circ$ ), is readily soluble in alcohol and ether, has a pleasant odour of oranges, and distils unaltered at  $262^\circ$ .

It yields nitro-, amino-, and hydroxy-derivatives. **p-Diamino-diphenyl-methane**,  $CH_2(C_6H_4NH_2)_2$ , is obtained by heating methylene-aniline,  $C_6H_5 \cdot N:CH_2$ , prepared from formaldehyde and aniline, with aniline and an aniline salt. It crystallizes in lustrous silvery plates, melting at  $87^\circ$ , and may be used for the preparation of fuchsine. Bromine at a moderate temperature reacts with the hydrocarbon yielding **diphenyl-bromomethane**,  $(C_6H_5)_2CHBr$ , and when this is heated with water to  $150^\circ$ , it yields **benzhydrol**, *diphenyl-carbinol*,  $(C_6H_5)_2CH \cdot OH$ , which can also be obtained from benzophenone and sodium amalgam, or by *Grignard's* synthesis from benzaldehyde and phenyl magnesium bromide (C. R., 1914, 158, 534). It crystallizes in glistening silky needles, melts at  $68^\circ$ , and as a secondary alcohol is readily oxidized to the corresponding ketone, benzophenone,  $(C_6H_5)_2CO$ .

**aa-Diphenyl-ethane**,  $(C_6H_5)_2CH \cdot CH_3$  (isomeric with dibenzyl, Chap. XXIX), is obtained by method of formation 2 (p. 546). It is a liquid, boils at  $286^\circ$ , and is oxidized to benzophenone by chromic acid. From it is derived:

**Benzilic acid**, *diphenyl-glycollic acid*,  $(C_6H_5)_2C(OH) \cdot CO_2H$ , which is formed by a molecular transformation when benzil,  $C_6H_5 \cdot CO \cdot CO \cdot C_6H_5$  (p. 550; also Chap. XXXVIII), is fused with potash. It crystallizes in needles or prisms, dissolves in concentrated sulphuric acid to a blood-red solution, and is reduced by hydriodic acid to **diphenyl-acetic acid**,  $(C_6H_5)_2CH \cdot CO_2H$  (needles or plates), which may also be obtained synthetically from phenyl-brom-acetic acid,  $C_6H_5 \cdot CHBr \cdot CO_2H$ , benzene, and zinc dust, according to mode of formation 1, p. 546.

**Benzoyl-benzoic acids**, benzophenone-carboxylic acids,  $C_6H_5 \cdot CO \cdot C_6H_4 \cdot CO_2H$ . Of these the *o*-acid (m.-pt.  $127^\circ$ ) has been prepared synthetically by heating phthalic anhydride with benzene and aluminium chloride. When heated with phosphorus pentoxide, at  $180^\circ$ , it yields anthra-quinone,



This is a typical reaction and is used for preparing many anthracene derivatives.

Fluorene, diphenylene-methane,  $\begin{array}{c} \text{C}_6\text{H}_4 \\ | \\ \text{C}_6\text{H}_4 \end{array} \text{CH}_2$ , stands in the

same relation to diphenyl-methane as carbazole (p. 543) does to diphenylamine; it is at the same time a diphenyl and a methane derivative. It is contained in coal-tar, and is produced when diphenyl-methane is led through red-hot tubes (like diphenyl from benzene), and also by passing the vapour of diphenylene-ketone over red-hot zinc dust. It crystallizes in colourless plates with a violet fluorescence, melts at  $113^\circ$ , and boils at  $295^\circ$ . The corresponding ketone, **diphenylene-ketone**,  $\text{C}_{12}\text{H}_8:\text{CO}$ , which crystallizes in yellow prisms melting at  $84^\circ$ , is obtained by heating phenanthra-quinone with lime, and is converted into **fluorenyl alcohol**,  $(\text{C}_6\text{H}_4)_2:\text{CH}\cdot\text{OH}$  (colourless plates, m.-pt.  $153^\circ$ ), by nascent hydrogen, and into **diphenyl-carboxylic acid**, *o*-**phenyl-benzoic acid**,  $\text{C}_6\text{H}_5\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H}$ , by fusion with potash.

## XXIX. DIBENZYL GROUP

This group comprises the compounds containing two benzene nuclei connected by a chain of two carbon atoms. Among the most important members are: Dibenzyl,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{C}_6\text{H}_5$ ; stilbene,  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_5$ ; tolane,  $\text{C}_6\text{H}_5\cdot\text{C}:\text{C}\cdot\text{C}_6\text{H}_5$ ; deoxybenzoin,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CO}\cdot\text{C}_6\text{H}_5$ ; hydrobenzoin,  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{C}_6\text{H}_5$ ; benzoin,  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CO}\cdot\text{C}_6\text{H}_5$ ; benzil,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CO}\cdot\text{C}_6\text{H}_5$ .

Dibenzyl is symmetrical diphenyl-ethane (for the unsymmetrical compound see p. 547), stilbene is *s*-diphenyl-ethylene, and tolane diphenyl-acetylene.

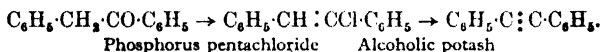
All these compounds yield benzoic acid when oxidized.

**Dibenzyl** is formed when benzyl chloride is treated with metallic sodium, or by the action of benzyl chloride on benzyl magnesium chloride. It is often met with as a by-product in *Grignard's* synthesis by means of benzyl magnesium chloride. It is isomeric with ditolyl and with tolyl-phenyl-methane; it crystallizes in needles or small plates, melts at  $52^\circ$ , and sublimes unchanged.

**Stilbene**, *s*-diphenyl-ethylene, forms monoclinic plates or

prisms, melts at  $125^{\circ}$ , and also boils without decomposition. It may be prepared by the action of sodium upon benzal chloride, or by heating deoxybenzoïn with sodium ethoxide, or best by the action of benzyl magnesium chloride on benzaldehyde, and possesses the full character of an olefine, giving, for instance, a dibromide,  $\text{C}_6\text{H}_5\cdot\text{CHBr}\cdot\text{CHBr}\cdot\text{C}_6\text{H}_5$ , with bromine, and being converted into dibenzyl by hydriodic acid. *p*-**Diamino-stilbene**,  $\text{C}_{14}\text{H}_{10}(\text{NH}_2)_2$ , and its disulphonic acid (obtained by reducing *p*-nitro-toluene or its sulphonic acid in alkaline solution) are, like benzidine, mother substances of "substantive dyes" (Chap. LIX, B2). Stilbene should exist in two stereo-isomeric modifications, the ordinary stilbene melting at  $125^{\circ}$  is usually regarded as the *trans* compound  $\text{H}\cdot\text{C}\cdot\text{Ph}$

$\text{Ph}\cdot\ddot{\text{C}}\cdot\text{H}$ . An isomeride—the *cis* compound has been described by Otto and Stoffel (B., 1897, 1799). Just as ethylene bromide yields acetylene when boiled with alcoholic potash, so stilbene dibromide yields **tolane**, which crystallizes in prisms or plates, melting at  $60^{\circ}$ . It may also be prepared by the following series of reactions:

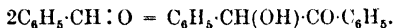


Tolane corresponds with acetylene in its properties in so far that it combines with chlorine to a dichloride and a tetrachloride; but it does not yield metallic derivatives, since it contains no "acetylene hydrogen" (p. 55).

When stilbene dibromide is treated with silver acetate, two di-acetates are formed; and when these are hydrolysed by alcoholic ammonia, two isomeric substances of the composition,  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{C}_6\text{H}_5$ , **hydrobenzoïn** and **iso-hydrobenzoïn** or *s*-**diphenyl-glycol**, are produced. Both compounds are also formed by the action of sodium amalgam upon oil of bitter almonds. The former crystallizes in rhombic plates, melting at  $138^{\circ}$ , and the latter in four-sided prisms, melting at  $119^{\circ}$ , and is the more soluble of the two. The two compounds are stereo-isomeric in the same manner as meso-tartaric and racemic acid, and *Erlenmeyer, Junr.*, has been able to resolve hydrobenzoïn, which corresponds with racemic acid, into two optically active components, by separating two different kinds of hemihedral crystals (A., 198, 115, 191; B., 1897, 1531).

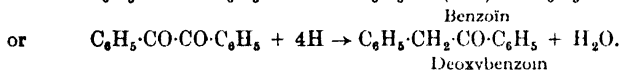
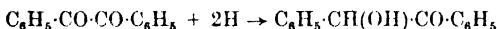


The compounds **benzoïn**, **benzil**, and **deoxybenzoïn**, which have already been mentioned, are closely related to one another, as their formulæ show, and can also be prepared from benzaldehyde. When the aldehyde is boiled with an alcoholic solution of potassium cyanide it polymerizes,\* yielding benzoïn,



This is often termed the **acyloïn** condensation, and is characteristic of many aromatic aldehydes and of furaldehyde (*J. A. C. S.*, 1932, 3302; 1933, 1228). Benzoïn forms glistening prisms, m.-pt. 134°; nascent hydrogen reduces it to hydrobenzoïn, from which it can also be obtained by oxidation. It reduces *Fehling's* solution even at the ordinary temperature, yielding benzil.

**Benzil**,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CO}\cdot\text{C}_6\text{H}_5$ , is obtained by oxidizing benzoïn with nitric acid. It crystallizes in large six-sided prisms, melting at 95°. It is oxidized to benzoic acid by chromic anhydride, and reduced by nascent hydrogen—according to the conditions—either to benzoïn or to deoxybenzoïn,



It reacts with hydroxylamine to produce:

**Benzil-monoxime**,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{C}(:\text{N}\cdot\text{OH})\cdot\text{C}_6\text{H}_5$ , and **benzil-dioxime**,  $\text{C}_6\text{H}_5\cdot\text{C}(:\text{N}\cdot\text{OH})\cdot\text{C}(:\text{N}\cdot\text{OH})\cdot\text{C}_6\text{H}_5$ , which exist in the following stereo-isomeric modifications (*Hantzsch* and *Werner*, *B.*, 1889, 11; 1904, 4295; *Dittrich*, *ibid.* 1891, 3267):

**Monoximes:**

*a.* M.-pt. 134°, *β.* M.-pt. 113°.

**Dioximes:**

*a.* M.-pt. 237°, *β.* M.-pt. 207°, *γ.* M.-pt. 163°,  
and possibly a fourth form.

For discussion on configurations see Chap. L, C1.

**Deoxybenzoïn**,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CO}\cdot\text{C}_6\text{H}_5$ , forms large plates, melting at 55°, and may be sublimed or distilled unchanged. It can be prepared by the action of benzene and aluminium

\* For mechanism cf. *Chalanay* and *Knoevenagel* *B.*, 1892, 295; *Lapworth*, *J. C. S.*, 1903, 1004.

chloride upon phenyl-acetyl chloride,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CO}\cdot\text{Cl}$ , and hence its constitution, and yields di-benzyl with hydriodic acid. Deoxybenzoïn can also be prepared from benzil and benzoïn (B., 1892, 1728). One of its methylene hydrogen atoms is readily replaceable by alkyl, just as in acetoacetic ester. The radical,  $\text{CH}(\text{C}_6\text{H}_5)\cdot\text{CO}\cdot\text{C}_6\text{H}_5$ , is termed "desyl".

**Benzilic acid**,  $(\text{C}_6\text{H}_5)_2\text{C}(\text{OH})\cdot\text{CO}_2\text{H}$  (p. 547), is formed when benzil is heated with alcoholic potash, by a peculiar molecular transformation similar to that by which pinacolone is formed (cf. Chap. XXXVIII).

Compounds closely related to the dibenzyl group are those which contain two benzene nuclei united by a chain of more than two carbon atoms, e.g.  $\alpha\gamma$ -diphenyl propane, and also those compounds containing three or more benzene nuclei united by a chain of carbon atoms, e.g. triphenyl-ethane, tetraphenyl-ethane, &c.

### XXX. TRIPHENYL-METHANE GROUP

Triphenyl-methane,  $\text{CH}(\text{C}_6\text{H}_5)_3$ , is the parent compound of the group, homologues are tolyl-diphenyl-methane,  $(\text{C}_6\text{H}_5)_2\text{CH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$ , ditolyl-phenyl-methane,  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{C}_6\text{H}_4\cdot\text{CH}_3)_2$ , &c.

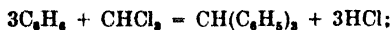
These hydrocarbons are of especial interest as being the mother substances of an extensive series of dyes; the amino-, hydroxy-, and carboxy-derivatives of triphenyl-methane are the leuco-bases obtained from such dyes as rosaniline, aurine, malachite green, &c.

Their *formation* is effected in a manner analogous to that of the diphenyl-methane derivatives, i.e. by the aid of zinc dust or aluminium chloride when chlorine compounds are used, or by the aid of phosphoric anhydride when oxygen compounds are employed.

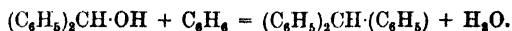
Thus, triphenyl-methane may be obtained (*a*) from benzal chloride and benzene in the presence of aluminium chloride,



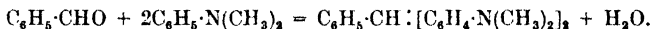
or from benzaldehyde, benzene, and zinc chloride; (*b*) from chloroform and benzene in presence of aluminium chloride,



(c) from benzhydrol and benzene in the presence of phosphoric anhydride,



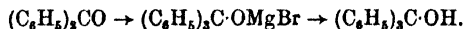
Derivatives of triphenyl-methane may be obtained by similar methods, e.g. the leuco-base of bitter-almond-oil green, tetramethyl-diamino-triphenyl-methane may be prepared by the condensation of benzaldehyde and dimethyl-aniline:



When other amines or even phenols are used, a series of allied compounds (which are often dyes) is obtained, the separation of water being facilitated by the addition of zinc chloride, concentrated sulphuric acid, or anhydrous oxalic acid.

**Triphenyl-methane**,  $\text{CH}(\text{C}_6\text{H}_5)_3$  (*Kekulé* and *Franchimont*), may be prepared from chloroform and benzene by the *Friedel-Crafts* reaction (cf. A., 194, 152), diphenyl-methane being produced at the same time; also by eliminating the amino-groups from *p*-leucaniline,  $\text{C}_{19}\text{H}_{13}(\text{NH}_2)_3$ , and most readily by reducing triphenyl-carbinol with zinc dust and acetic acid. It crystallizes in colourless prisms, m.-pt.  $93^\circ$ , b.-pt.  $359^\circ$ , and dissolves readily in hot alcohol, ether, or benzene.

Like many of its derivatives it crystallizes with 1 Mol.  $\text{C}_6\text{H}_6$ . With a carbon disulphide solution of bromine it yields **triphenyl-methyl bromide**,  $(\text{C}_6\text{H}_5)_3\text{CBr}$ , which, when boiled with water, yields **triphenyl-carbinol**,  $(\text{C}_6\text{H}_5)_3\text{C}\cdot\text{OH}$ . This crystallizes in glistening prisms, melts at  $159^\circ$ , and can be sublimed unchanged; it may also be prepared directly by oxidizing a solution of triphenyl-methane in glacial acetic acid with chromic acid, or synthetically by the action of *Grignard's* phenyl magnesium bromide on benzophenone or ethyl benzoate:



A number of homologous and substituted triphenyl-carbinols have been prepared by this last method (*Houben*, B., 1903, 3087), and also by the reaction between an amino-arylketone, sodium and an aryl halide, the sodium first forming a compound of the type  $\text{R}_2\cdot\text{CNa}\cdot\text{ONa}$ , which reacts with the arylhalide yielding  $\text{R}_2\cdot\text{CR}'\cdot\text{ONa}$  (*Rodd and Lynch*, J. A. C. S., 1927, 2174).

**Triphenyl-methylamine**,  $\text{CPh}_3\cdot\text{NH}_2$  (B., 1912, 2910), resembles the carbinol in the readiness with which the  $\text{NH}_2$  can

be replaced, e.g. with ethyl alcohol the  $\text{NH}_2$  is replaced by  $\text{OEt}$ .

Fuming nitric acid converts triphenyl-methane into **trinitro-triphenyl-methane**,  $(\text{C}_6\text{H}_4\cdot\text{NO}_2)_3\cdot\text{CH}$  (yellow scales), which can then be oxidized by chromic acid to **trinitro-triphenyl-carbinol**,  $(\text{C}_6\text{H}_4\cdot\text{NO}_2)_3\text{C}\cdot\text{OH}$ . The latter gives para-rosaniline,  $(\text{C}_6\text{H}_4\cdot\text{NH}_2)_3\text{C}\cdot\text{OH}$ , when reduced with zinc dust and glacial acetic acid.

Homologous with triphenyl-methane are the **tolyl-diphenyl-methanes**,  $(\text{C}_6\text{H}_5)_2\text{CH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$ . From these also dyes are derived, especially from *m*-**tolyl-diphenyl-methane** (in which the  $\text{CH}_3$  occupies the meta-position with regard to the methane carbon atom), which can be prepared by diazotizing ordinary leucaniline; it crystallizes in small prisms and melts at  $59\cdot5^\circ$ .

### TRIPHENYL-METHANE DYES

The entrance of three amino- or hydroxy-groups converts triphenyl-methane and its homologues into the leuco-compounds of dyes, some of which latter are of great value. Two amino-groups suffice for the full development of the dye character only when the amino-hydrogen atoms are replaced by alkyl radicals, one amino-group being insufficient for this (see under *p*-amino-triphenyl-methane).

The following are the chief groups of triphenyl-methane dyes:

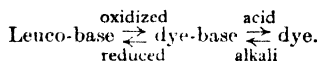
1. Those derived from diamino-triphenyl-methane. The malachite-green group.
2. Those derived from triamino-triphenyl-methane. The rosaniline group.
3. Those derived from trihydroxy-triphenyl-methane. The aurine group.
4. Those derived from triphenyl-methane-carboxylic acid. The eosin group.

**Leuco-bases** or **leuco-compounds** of dyes (Chap. XXII, E.) are the colourless compounds formed by the reduction of the dyes, usually by the addition of two atoms of hydrogen. When oxidized they are converted back into the dyes.

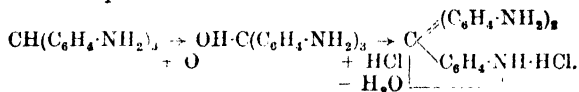
All the dyes of the triphenyl-methane group, and also indigo, methylene blue, safranine, &c., are capable of yielding such leuco-compounds, generally on reduction with zinc and hydrochloric acid, stannous chloride, or ammonium sulphide.

The oxidation of the leuco-compounds is often quickly effected by the oxygen of the air (e.g. in the cases of indigo white and of leuco-methylene blue); in the triphenyl-methane group it is slower and frequently more complicated. Leuco-malachite green is readily oxidized to the corresponding colour-base when treated with lead peroxide in acid solution, and leucaniline when warmed with chloranil in alcoholic solution, or when its hydrochloride is heated either alone or with a concentrated solution of arsenic acid, or with metallic hydroxides such as ferric hydroxide.

The leuco-bases of the triphenyl-methane dyes are derivatives of triphenyl-methane or its homologues, the corresponding dye-bases obtained by oxidizing the leuco-bases are derivatives of triphenyl-carbinol or its homologues, and the dyes themselves are salts obtained by the elimination of water from the dye-base and an acid. The relationships between the three groups of compounds—leuco-base, dye-base, and dyes—are indicated in the following scheme:



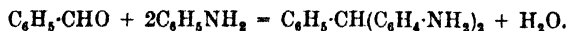
As an example:



#### 1. AMINO- AND DIAMINO- TRIPHENYL-METHANE GROUP

***p*-Amino-triphenyl-methane** can be synthesized either by the condensation of *p*-nitro-benzaldehyde with benzene and subsequent reduction, or from benzhydrol and aniline. It forms large prisms, and melts at 84°. The corresponding carbinol is colourless and with acids yields red salts, but these cannot dye animal fibres. (Cf., however, B., 1913, 70.)

***p*:*p*-Diamino-triphenyl-methane**,  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{C}_6\text{H}_4\cdot\text{NH}_2)_2$ , is prepared by the action of zinc chloride or of fuming hydrochloric acid upon a mixture of benzaldehyde and aniline sulphate or chloride:



It crystallizes in prisms, and the colourless salts yield an

unstable blue-violet dye, benzal violet, when oxidized. Methylation converts the base into:

**Tetramethyl-di-*p*-amino-triphenyl-methane**, *leuco-malachite green*,  $C_6H_5 \cdot CH[C_6H_4 \cdot N(CH_3)_2]_2$ , which is prepared on the technical scale by heating benzaldehyde and dimethyl-aniline with zinc chloride or concentrated sulphuric acid (*O. Fischer*, A., 206, 103). It forms colourless plates or prisms. As a diacid base it yields colourless salts, which are slowly converted by the air, but immediately by other oxidizing agents, such as lead dioxide and sulphuric acid, into the salts of **tetramethyl-diamino-triphenyl-carbinol**,  $C_6H_5 \cdot C(OH)[C_6H_4N(CH_3)_2]_2$ . The free base is obtained by precipitating the salts with alkali. It crystallizes in colourless needles, and dissolves in cold acid to a colourless solution; upon warming, however, the intense green coloration of the salts is produced (see p. 557).

The double salt with zinc chloride,  $(C_{23}H_{25}N_2Cl)_3 \cdot 2ZnCl_2 \cdot 2H_2O$ , or the oxalate,  $(C_{23}H_{25}N_2)_2 \cdot 3H_2C_2O_4$ , of this base is the valuable dye **bitter-almond-oil green**, *malachite green* or *Victoria green*, which forms green plates, readily soluble in water. This can also be prepared directly by heating benzo-trichloride with dimethyl-aniline and zinc chloride (*Doebner*). **Brilliant green** is the tetrachyl compound. The sulphonic acid of the diethyl-dibenzyl-diamino-triphenyl-carbinol is **acid green**.

The fastness of all these dyes is improved by the introduction of an ortho-chlorine atom. Sulphonic acids derived from these chloro-compounds are the **night green**, A., **patent green**, A. G. L., and **brilliant milling green** of commerce.

## 2. ROSANILINE GROUP

Fuchsine or magenta was first obtained in 1856 by *Natanson*, who noticed the formation of a red substance, in addition to that of aniline hydrochloride and ethylene-aniline, when ethylene chloride was allowed to act upon aniline at a temperature of  $200^\circ$  (A., 98, 297). It was prepared shortly afterwards by *A. W. Hofmann*, by the action of carbon tetrachloride upon aniline, and was first manufactured on the technical scale in 1859. *Hofmann's* scientific researches on this subject date from 1861. The chemical constitution was made clear by *Emil* and *Otto Fischer* (1878).

The rosaniline dyes are derived partly from triphenyl-methane and partly from *m*-tolyl-diphenyl-methane; in the

former case they are often designated *para*-compounds (e.g. "para-rosaniline", because it is prepared from aniline and para-toluidine; "para-rosolic acid").

**Para-leucaniline**, *triamino-triphenyl-methane*,  $\text{CH}(\text{C}_6\text{H}_4\cdot\text{NH}_2)_3$ , and **leucaniline**, *triamino-diphenyl-tolyl-methane*,  $\text{CH}_3\cdot\text{C}_6\text{H}_3(\text{NH}_2)\cdot\text{CH}(\text{C}_6\text{H}_4\cdot\text{NH}_2)_2$ , are formed by the reduction of the corresponding trinitro-compounds and also of the corresponding dye-bases, para-rosaniline and rosaniline; the first named also by the reduction of *p*-nitro-diamino-triphenyl-methane. The free leuco-bases are precipitated by ammonia from solutions of their salts as white or reddish flocculent masses, and crystallize in colourless needles or plates; they melt at  $203^\circ$  and  $100^\circ$  respectively. As bases they form colourless crystalline salts.

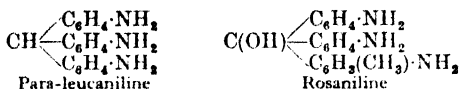
**Para-rosaniline**,  $\text{OH}\cdot\text{C}(\text{C}_6\text{H}_4\text{NH}_2)_3$ , and **rosaniline**,  $\text{OH}\cdot\text{C}(\text{C}_6\text{H}_4\cdot\text{NH}_2)_2$ , are the bases of the magenta dyes. They

$\text{C} \begin{array}{l} \nearrow \text{C}_6\text{H}_4\text{Me}\cdot\text{NH}_2 \\ \searrow \end{array}$ , are the bases of the magenta dyes. They are obtained by precipitating solutions of their salts with alkalis, and crystallize from hot water or alcohol in colourless needles or plates, which become red in the air. Both are tri-acid bases, stronger than ammonia. As they yield tri-diazonium salts on treatment with nitrous acid, they must contain three primary amino-groups. The diazonium compounds readily yield the corresponding hydroxylic dyes, aurine and rosolic acid (this Chap., 3), when boiled with water.

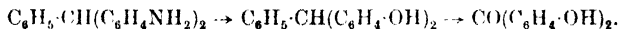
*Constitution.*—The relations between the rosanilines and triphenyl-methane were made clear by *Emil* and *Otto Fischer*, who transformed leucaniline into diphenyl-tolyl-methane by diazotizing and decomposing with alcohol. In a similar manner, para-leucaniline was converted into triphenyl-methane. The two leuco-bases are, therefore, undoubtedly triamino-derivatives of diphenyl-*p*-tolyl-methane and of triphenyl-methane respectively. The dye-bases, which differ from the leuco-bases by one atom of oxygen, are the corresponding carbinol derivatives, i.e. rosaniline is triamino-diphenyl-*p*-tolyl carbinol, and para-rosaniline triamino-triphenyl-carbinol.

That the three amino-groups are distributed equally among the three benzene nuclei is clear from the synthesis of para-leucaniline by means of *p*-nitro-benzaldehyde. *p*-Nitro-benzaldehyde, aniline, and sulphuric acid yield *p*-nitro-diamino-triphenyl-methane,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}(\text{C}_6\text{H}_4\cdot\text{NH}_2)_2$ , which,

when reduced, yields para-leucaniline. We have, therefore, the following formulæ:



It can be shown that each amino-group occupies the *p*-position with respect to the methane carbon atom. Diamino-triphenyl-methane can be synthesized from benzaldehyde and aniline in the presence of a dehydrating agent. When diazotized and warmed with water, the corresponding dihydroxy-triphenyl-methane is formed, and this, when fused with potash, yields *p*-dihydroxy-benzophenone:

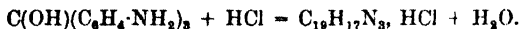


In this last compound the *p*-positions of the hydroxy-groups have been established, and hence the original amino-groups must also have occupied the *p*-positions, unless intramolecular rearrangement has occurred.

When *p*-nitro-benzaldehyde is condensed with aniline, *p*-nitro-diamino-triphenyl-methane is formed, and the nitro-group must be in the *p*-position, and by analogy with the previous reaction the two amino-groups are also in *p*-positions, and as this compound on reduction yields para-leucaniline it follows that all three amino-groups occupy *p*-positions—a conclusion which is supported by the fact that para-leucaniline can also be transformed into *p*-dihydroxy-benzophenone.

The salts of rosaniline and para-rosaniline, **fuchsine** or magenta,  $\text{C}_{20}\text{H}_{20}\text{N}_3\text{Cl}$ , **rosaniline nitrate**,  $\text{C}_{20}\text{H}_{20}\text{N}_3(\text{NO}_3)$ , **rosaniline acetate**,  $\text{C}_{20}\text{H}_{20}\text{N}_3(\text{C}_2\text{H}_3\text{O}_2)$ , **para-fuchsine**,  $\text{C}_{19}\text{H}_{18}\text{N}_3\text{Cl}$ , &c., are the actual dyes. While they possess a magnificent magenta-red colour in solution, and have intense colouring power (dyeing wool and silk without a mordant), their crystals are of a brilliant metallic green with cantharides lustre, i.e. of nearly the complementary colour. They are fairly soluble in hot water and alcohol.

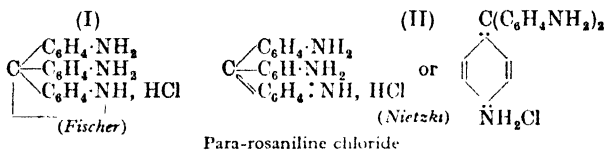
In the formation of the salts, water is eliminated:



In the dyes there is therefore present a peculiar nitrogen-carbon linking (see Formula I), which is reminiscent of the older quinone formula; but the simpler constitution (Formula



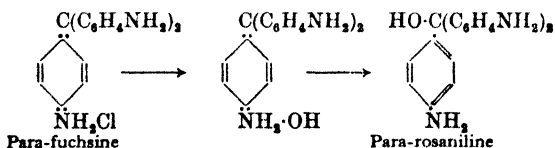
II), which corresponds with the newer quinone formula, is now more generally accepted, and is usually termed the quinonoid formula:



An analogous separation of water is also observed in the formation of salts of the malachite green base, but this only takes place upon warming, as is proved by the fact that it dissolves without colour in cold acids, and that the intense coloration of the salts first becomes apparent after warming the solution.

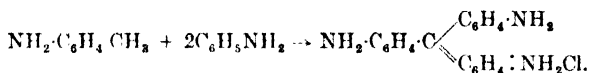
In addition to the above salts there also exist acid ones, e.g.  $\text{C}_{20}\text{H}_{20}\text{N}_3\text{Cl} + 3\text{HCl}$  (which yields a yellow-brown solution, not a magenta-coloured one); these dissociate into the neutral salts and free acid upon the addition of much water. The formation of such acid salts is readily accounted for by the quinonoid formula.

Assuming the quinonoid structure II for para-fuchsine, then the conversion into para-rosaniline under the influence of alkalis should be preceded by the formation of an unstable quaternary ammonium hydroxide, which becomes transformed into the carbinol compound, para-rosaniline:



*Hantzsch* and *Osswald*, by means of electrical conductivity determinations (B., 1900, 278), have been able to indicate the presence of such an ammonium derivative in the solution which is formed when the dye is brought into contact with an equivalent of alkali. This compound is coloured in contradistinction to the carbinol base, is very strongly basic and therefore strongly ionized, and is gradually transformed into the insoluble carbinol base. Para-rosaniline and the dye-bases generally are pseudo-bases corresponding in many respects with the pseudo-acids (p. 425).

Formerly in the manufacture of magenta, a mixture of aniline with *o*- and *p*-toluidine was oxidized by syrupy arsenic acid, stannic chloride or mercuric chloride or nitrate, &c.; in the modern method, a mixture of nitro-benzene with aniline and toluidine is heated with iron filings and hydrochloric acid (*Coupler*). Nitro-toluene may also be employed instead of nitro-benzene. If *o*-toluidine is present in the mixture of aniline and *p*-toluidine to be oxidized, rosaniline is formed, and if it is absent, para-rosaniline. When pure aniline is oxidized alone, it yields no fuchsine at all, but products of the nature of indulin. This is explained by the fact that for the formation of fuchsine a carbon atom is required which shall serve to link the benzene nuclei together, a so-called "methane-carbon"; in the action of carbon tetrachloride upon aniline, this carbon originates from the tetrachloride, and in the oxidation of a mixture of aniline and *p*-toluidine, from the methyl group of the latter, as is shown in the following scheme:



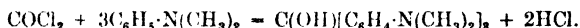
Para-rosaniline and rosaniline are also formed by heating *p*-diamino-diphenyl-methane (p. 547) with aniline and *o*-toluidine respectively, in presence of an oxidizing agent (B., 1892, 302).

When rosaniline is heated with hydrochloric or hydriodic acid to 200°, it is split up into aniline and toluidines; when superheated with water, para-rosaniline yields *p*-dihydroxy-benzophenone, ammonia, and phenol. When boiled with hydrochloric acid, rosaniline breaks up into *p*-diamino-benzophenone and *o*-toluidine. A solution of fuchsine is decolorized by sulphurous acid, an additive-product, fuchsine-sulphurous acid, being formed. This solution, *Schiff's* reagent, is a delicate reagent for aldehydes, which colour it violet-red (see p. 150).

Formaldehyde and *o*-toluidine yield methylene *o*-toluidine,  $\text{CH}_2\text{:N}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$ , which condenses with *o*-toluidine and its hydrochloride, yielding diamino-*o*-tritolylmethane, which can be oxidized to the dye **new magenta**.

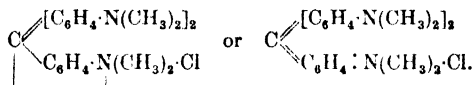
1. **Methylated rosanilines** (*Hofmann, Lauth*).—The red colour of para-rosaniline and of rosaniline is changed into violet by the entrance of methyl or ethyl groups, the intensity of the latter colour increasing with an increasing number of these groups. The salts of **hexamethyl-para-rosaniline** have

a magnificent bluish-violet shade. In the manufacture of these "**methyl-violets**" one may either (1) methylate rosaniline (by means of  $\text{CH}_3\text{Cl}$  or  $\text{CH}_3\text{I}$ ); or (2) oxidize, instead of aniline, a methylated aniline such as dimethyl-aniline by means of **cupric** salts, whereby para-rosaniline derivatives result; or (3) allow phosgene to act upon dimethyl-aniline (or the latter to act upon the tetramethyl-diamino-benzophenone first produced):



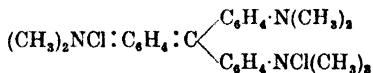
In the last case hexamethyl-violet, termed "**crystal violet**" on account of the beauty of its crystals, is formed, while the methyl-violets prepared by methods (1) and (2) are mixtures of hexa-, penta-, and tetramethyl-rosanilines and are amorphous.

The hydrochloride of the hexamethyl dye has the constitution:



An interesting synthesis of this compound is by the action of the magnesium derivative of *p*-bromo-dimethyl-aniline on tetramethyl-diamino-benzophenone and subsequent treatment with hydrochloric acid (cf. Synthesis of Tertiary Alcohols, p. 141).

The hexamethyl-carbinol no longer contains an amino-hydrogen atom, in consequence of which any further methyl chloride or iodide cannot effect an exchange of hydrogen for alkyl, but can only form an additive compound, a quaternary ammonium salt. Such addition causes a change of colour from violet to green; thus the compound



is the dye **methyl green** or *light green*. **Ethyl green** (ethyl-hexamethyl rosaniline) is formed by the action of ethyl bromide on methyl violet.

Various **ethyl violets** are known corresponding with the methyl violets. The hexa-substituted rosanilines, which contain benzyl as well as methyl or ethyl groups, are similar to crystal violet; their sulphonic acids form useful dyes, e.g. **acid violet**.

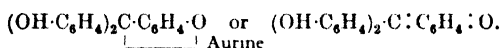
**2. Phenylated rosanilines.** By the successive entrance of

phenyl-groups into rosaniline, there are formed in the first instance violet dyes, which change to blue when three phenyl groups have entered. **Triphenyl-fuchsine** or "**aniline blue**" is a beautiful blue dye, insoluble in water but soluble in alcohol. It is prepared by heating rosaniline with aniline in presence of benzoic acid, when ammonia is eliminated; or by the oxidation of phenylated aniline, i.e. diphenylamine, e.g. by means of oxalic acid. The latter supplies the "methane carbon atom", and the beautiful "diphenylamine blue" or **spirit blue** which is formed is a para-rosaniline derivative. Formaldehyde can also supply the methane carbon atom.

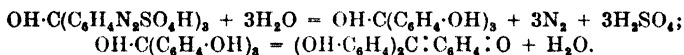
Dyes insoluble in water are converted into soluble sulphonic acids. Such acids are **Nicholson's blue**, **water blue**, and **light blue**. **Patent blue**, **new patent blue**, are disulphonic acids.

### 3. TRIHYDROXY-TRIPHENYL-METHANE, $\text{CH}(\text{C}_6\text{H}_4\cdot\text{OH})_3$ , OR THE AURINE GROUP

The hydroxy-analogues of para-rosaniline and rosaniline are **aurine**,  $\text{C}_{19}\text{H}_{14}\text{O}_3$ , and **rosolic acid**,  $\text{C}_{20}\text{H}_{16}\text{O}_3$ :



They are acid (phenol dyes) not basic dyes and are of far less value than the basic dyes already described. They are formed when the diazonium derivatives of para-rosaniline or rosaniline are boiled with water (*Caro and Wanklyn*, 1866):



The primary product, carbinol, is incapable of existence, and loses water. The constitutional formulæ follow from this close relation to the rosanilines.

Aurine is also obtained by heating phenol with oxalic and sulphuric acids to 130°–150° (*Kolbe and Schmitt*, 1859), the oxalic acid yielding the "methane carbon atom"; rosolic acid results in an analogous manner from a mixture of phenol and cresol with arsenic and sulphuric acids. Phenol by itself yields no rosolic acid upon oxidation.

Aurine and rosolic acid crystallize in beautiful green needles or prisms with a metallic lustre, dissolve in alkalis with a magenta red colour, and are thrown down again from this solution by acids. The alkaline salts are decidedly unstable,

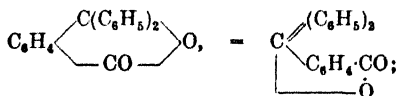
aurine being but a weak phenol; at the same time it possesses a slightly basic character. An ammonium salt is known which crystallizes in dark-red needles with a blue lustre. Upon reduction there are formed the leuco-compounds **leucaurine**,  $\text{CH}(\text{C}_6\text{H}_4\cdot\text{OH})_3$ , and **leuco-rosolic acid**,  $\text{OH}\cdot\text{C}_6\text{H}_3\text{Me}\cdot\text{CH}(\text{C}_6\text{H}_4\cdot\text{OH})_2$ , both of which crystallize in colourless needles of phenolic character. Superheating with water transforms aurine into *p*-dihydroxy-benzophenone,  $\text{CO}(\text{C}_6\text{H}_4\cdot\text{OH})_2$ , and phenol; superheating with ammonia, into para-rosaniline.

**Chrome violet**, prepared from formaldehyde, salicylic acid, and sulphuric acid, is sodium aurine-tricarboxylate.

#### 4. TRIPHENYL-METHANE-CARBOXYLIC ACID, OR THE EOSIN GROUP

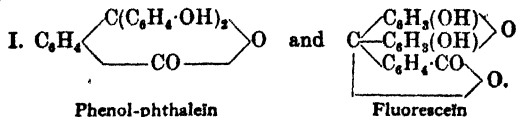
**Triphenyl-methane-carboxylic acid**,  $\text{CH}(\text{C}_6\text{H}_5)_2(\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H})$ , obtained by the reduction of phthalophenone (see below), crystallizes in colourless needles melting at  $162^\circ$  and yields triphenyl-methane by the elimination of carbon dioxide.

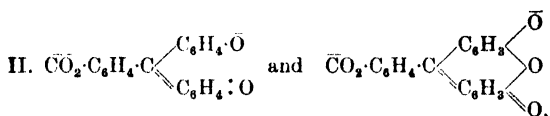
**Triphenyl-carbinol-*o*-carboxylic acid**,  $\text{OH}\cdot\text{C}(\text{C}_6\text{H}_5)_2(\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H})$ . The anhydride of this acid, **phthalophenone**, obtained by heating phthalyl chloride with benzene and aluminium chloride, forms plates, melting at  $115^\circ$ . The acid itself is incapable of existence, but its salts are obtained by dissolving the anhydride in alkalis. Phthalophenone is on the one hand a triphenyl-methane derivative and on the other a derivative of phthalic acid; in accordance with the constitutional formula:



it is to be regarded as diphenyl-phthalide (Phthalide, Chap. XXVI, A4).

The hydroxy- and amino-derivatives of phthalophenone are important dyes. The hydroxy compounds are prepared by the action of phenols upon phthalic anhydride, and are termed *Phthaleïns*. Phenol and resorcinol, for example, yield the compounds:

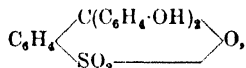




Free phenolphthalein, which is colourless, has the lactone structure I. The acid solutions are also colourless, whereas the dialkali salts are intensely coloured, and the divalent anion undoubtedly has the quinonoid structure II. Phenolphthalein is used as an indicator in acidimetry, the change in colour occurring at  $p_{\text{H}}$  8.4.

A large excess of alkali transforms the coloured salts into colourless ones, probably  $\text{CO}_2\text{Na}\cdot\text{C}_6\text{H}_4\cdot\text{C}(\text{OH})(\text{C}_6\text{H}_4\cdot\text{ONa})_2$ .

**Sulphonephthaleins** are analogous derivatives of the *o*-sulphonic acid, e.g.



which is used as an indicator. The bivalent ion formed at  $p_{\text{H}}$  7.9 is deep red.

In the case of fluorescein a molecule of water is split off from two hydroxyls of the two resorcinol residues. Phthaleins as hydroxy-phthalophenones are converted by reduction into the hydroxy-derivatives of triphenyl-methane-carboxylic acid, which are termed "*Phthalines*"; e.g. phenolphthalein into dihydroxy-triphenyl-methane-carboxylic acid (i.e. phenol-

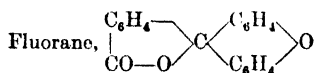
phthaline),  $\text{CH} \begin{array}{l} \diagup (\text{C}_6\text{H}_4\cdot\text{OH})_2 \\ \diagdown \text{C}_6\text{H}_4\cdot\text{CO}_2\text{H} \end{array}$ . The phthalines are colourless,

and are to be looked upon as leuco-compounds of the phthaleins. The phthaleins include many dyes which are of technical value, e.g. the eosins (*Caro, Baeyer, 1871*).

**Phenol-phthalein** is prepared by heating phthalic anhydride with phenol and sulphuric acid, or better, stannic chloride (or oxalic acid), to  $115^\circ$ – $120^\circ$ . It may also be obtained by nitrating diphenyl-phthalide, reducing the two substituting nitro-groups, and replacing the amino-groups thus formed by hydroxyl in the usual manner. It crystallizes from alcohol in colourless crusts; is nearly insoluble in water, but dissolves in dilute alkalis with a beautiful red colour which vanishes again on neutralization with acids; it is thus a valuable indicator. With very concentrated alkalis phenol-phthalein yields colour-

less solutions (cf. p. 563). A colourless and a red ethyl derivative are known corresponding with the lactone and quinone structures. The *p*-positions of the two hydroxy-groups have been proved by conversion into *p*-dihydroxy-benzophenone. It yields a **di-acetyl** derivative melting at  $143^{\circ}$  and an **oxime** melting at  $212^{\circ}$ . It is reduced by potash and zinc dust to **phenol-phthaline** (colourless needles), which dissolves in alkali to a colourless solution, but is readily reoxidized in this solution to phenol-phthaleïn. When treated with magnesium methyl iodide it does not show the presence of active hydrogen atoms, whereas fluoresceïn contains two active hydrogen atoms (G., 1912, **42**, ii, 204).

**Fluorane**,  $C_{20}H_{12}O_3$ , is formed as a by-product in the phenol-phthaleïn melt, and is the mother substance of fluoresceïn, and like pyrone can give rise to oxonium salts. The whole group of dyes is often known as the **Pyronine** group.

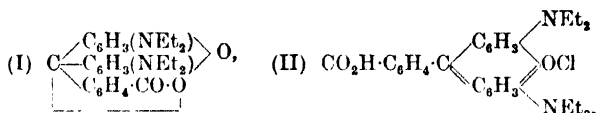


**Fluoresceïn**, *Dihydroxy-fluorane* or *resorcinol-phthaleïn*,  $C_{20}H_{12}O_5 + H_2O$ , is prepared by heating phthalic anhydride and resorcinol at  $200^{\circ}$ . It forms a dark-red crystalline powder, and dissolves in alcohol with a yellow-red colour, and in alkalis with a red colour and splendid green fluorescence. It is reducible to the phthaline "Fluoresceïn", and with bromine yields red crystals of tetrabromo-fluoresceïn, the potassium salt of which,  $C_{20}H_6Br_4O_5K_2$ , is the magnificent dye **eosin**. Fluorescing dyes are likewise formed in an analogous manner from all the derivatives of 1:3-dihydroxy-benzene, in which position 5 is unoccupied, and the reaction is often made use of on the one hand for testing for *m*-dihydroxy-derivatives, and on the other for phthalic anhydride or succinic anhydride.

Instead of phthalic acid itself, chlorinated or brominated, &c., phthalic acids may be employed, so that, by gradually increasing the amount of halogen present, a whole series of yellow-red to violet-red eosins can be prepared, e.g. tetrabromo-di-iodo-eosin; these are known under the names of Erythrosin, Rose de Bengale, Phloxin, &c. It is worthy of note that many

other dibasic acids (e.g. succinic) and also benzoic acid are capable of yielding fluorescing compounds. **Gallein**,  $C_{20}H_{12}O_7$ , is the dye obtained from pyrogallol and phthalic anhydride.

The **rhodamines** are dyes closely allied to fluorescein. They are obtained by the condensation of phthalic anhydride and *p*-alkylated-amino-phenols in presence of sulphuric acid. They contain the pyrone ring, and may be regarded as fluorescein in which the two hydroxyl groups have been replaced by tertiary amino-groups. **Tetra-ethyl rhodamine (I)**,



is colourless, and has basic properties. The salts, e.g. chloride, **Rhodamine B**, are red dyes, and probably possess either a quinonoid or oxonium (II) structure (Chap. LIX, E.).

**Tetraphenyl-methane**,  $C(C_6H_5)_4$ .—Triphenyl-bromo-methane and phenyl-hydrazine yield  $CPh_3 \cdot NH \cdot NPh$ , triphenylmethane-hydrazobenzene, which gives the corresponding azo-compound when oxidized,  $CPh_3 \cdot N : NPh$ , and when this is heated nitrogen is evolved and tetraphenyl-methane is formed. It is more readily prepared by the action of magnesium phenyl bromide on triphenyl-chloro-methane (B., 1906, 1462), and forms colourless crystals, melting at  $282^\circ$ .

*s*-**Tetraphenylethane**,  $CHPh_2 \cdot CHPh_2$ , is readily synthesized by the action of benzenediazonium sulphate on copper acetylide,  $4N : NPhSO_4H + 2CuC \equiv CCu \rightarrow CHPh_2 \cdot CHPh_2 + 4CuSO_4$ ; diphenyl is formed as a by-product (J. russ., 1916, 48, 253).

### XXXI. COMPOUNDS WITH CONDENSED BENZENE NUCLEI. NAPHTHALENE GROUP

The higher fractions of coal-tar contain hydrocarbons of high molecular weight, especially naphthalene,  $C_{10}H_8$ , anthracene,  $C_{14}H_{10}$ , and its isomeride phenanthrene. The first-named is found in the fraction between  $180^\circ$ – $200^\circ$ , and the two latter in that between  $340^\circ$ – $360^\circ$ .



These compounds are of more complex composition than benzene, the molecule of naphthalene differing from that of the latter by  $C_4H_2$ , and those of anthracene and phenanthrene from that of naphthalene by the same increment. They closely resemble benzene as regards behaviour, and give rise to types of derivatives similar to those of benzene itself.

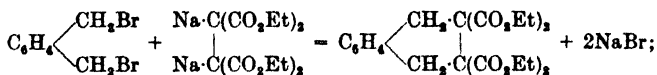
They undoubtedly contain benzene nuclei, as anthracene yields benzoic acid upon oxidation, naphthalene phthalic acid, and phenanthrene diphenic acid.

### A. Naphthalene

**Naphthalene**,  $C_{10}H_8$ , discovered by *Garden* in 1820, is contained in coal-tar and crystallizes from the fraction boiling at  $180^\circ$ – $200^\circ$ . The crystals are pressed to remove oily impurities, and are further purified by treatment with small amounts of concentrated sulphuric acid and subsequent sublimation.

It is also formed when various carbon compounds are subjected to a red heat; thus, together with benzene, styrene, &c., by passing the vapours of methane, ethylene, acetylene, alcohol, acetic acid, &c., through red-hot tubes. Naphthalene derivatives are formed when many sesquiterpenes (*Chap. LVII, F.*) are heated with sulphur. The constitutional formula is largely based on the following syntheses:

1. By the action of *o*-xylylene bromide upon the sodium compound of the symmetrical ethane-tetracarboxylic ester, **ethyl tetrahydronaphthalene-tetracarboxylate** is formed:

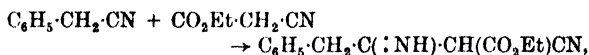


and from this, naphthalene may be obtained by hydrolysis, the elimination of the carboxyl groups and subsequent dehydrogenation (*Baeyer and Perkin, B., 1884, 448*).

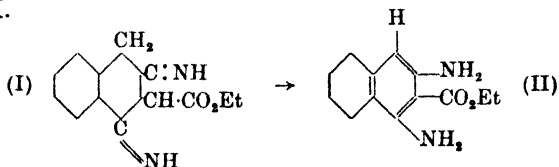
2.  $\alpha$ -Naphthol,  $C_{10}H_7 \cdot OH$ , is produced by the elimination of water from  $\gamma$ -phenyl-isocrotonic acid (*Fittig and Erdmann, cf. p. 567*), and yields naphthalene when heated with zinc dust.

3. *J. F. Thorpe* (*P., 1905, 21, 305*) has succeeded in synthesizing a number of naphthalene derivatives by means of ethyl sodio-cyano-acetate, e.g. ethyl 1:3-diamino-naphtha-

lene-2-carboxylate from ethyl sodio-cyano-acetate and benzyl cyanide.



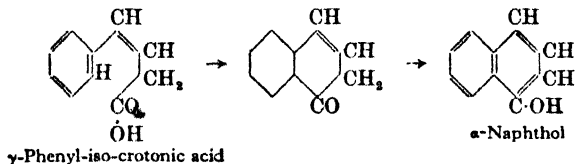
and this with sulphuric acid yields the bicyclic compound I, which is immediately transformed into the diamino-derivative II.



The same compound may be synthesized from ethyl sodio-cyano-acetate by the following stages (J. C. S., 1907, 578). Condensed with *o*-toluoyl chloride,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{Cl}$ , it yields ethyl cyano-*o*-toluyl-acetate,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{CH}(\text{CN})\text{CO}_2\text{Et}$ , and this when heated with ammonium acetate gives the corresponding imino-derivative,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{C}(:\text{NH})\cdot\text{CH}(\text{CN})\text{CO}_2\text{Et}$ , ethyl  $\beta$ -imino- $\alpha$ -cyano- $\beta$ -*o*-tolyl-propionate, which reacts with acids giving compound I.

1:4-Naphthalene-diamines have been prepared by similar methods, using derivatives of phenyl-butyric acid (J. C. S., 1907, 1004).

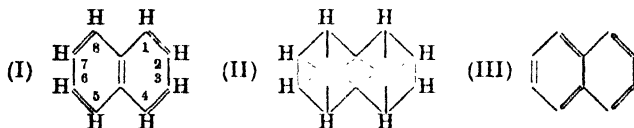
*Constitution.*—That naphthalene contains a benzene nucleus, in which two hydrogen atoms occupying the ortho-position are replaced by the group  $(\text{C}_4\text{H}_4)''$ , follows not only from its oxidation to phthalic acid, but also from its formation from *o*-xylylene bromide. And that the four carbon atoms of this group are linked to one another without branching is shown by the formation of  $\alpha$ -naphthol.



That there are actually two so-called "condensed" benzene nuclei present in the naphthalene molecule is a conclusion drawn from experiments of the following type:

$\alpha$ -Nitro-naphthalene (p. 571) on oxidation yields nitrophthalic acid,  $C_6H_3(NO_2)(CO_2H)_2$ ; consequently the benzene ring to which the nitro-group is linked remains intact. But, on reducing the nitro-naphthalene to amino-naphthalene and oxidizing the latter, no amino-phthalic acid nor any oxidation product of it is obtained, but phthalic acid itself, a proof that this time the benzene nucleus to which the amino-group is attached has been destroyed, and that the other has remained intact (*Graebe*, 1880; cf. also A., **149**, 20).

Naphthalene therefore receives the constitutional formula I (*Erlenmeyer*, 1866). There is the same difficulty in deciding between the double bond formula and the centric formula II (*Bamberger*) as in the case of benzene; and probably formula III suggested by *Harries* (A., 1905, **343**, 311), is most in harmony with the behaviour of naphthalene on oxidation and reduction, and involves less strain in the ring, but the physical and chemical properties do not lead to any definite conclusion (cf. C. and I., 1933, 161; J. A. C. S., 1935, 1459).



The above constitutional formula is in complete harmony with the number of isomeric forms in which naphthalene derivatives occur, and also with the formation of additive compounds with hydrogen or chlorine.

This union of two benzene nuclei is accompanied by a modification of their properties, so that naphthalene and its derivatives differ characteristically from benzene in many respects. Such differences show themselves, for instance, between the naphthylamines and aniline, the naphthols and phenol; and also especially in the greater readiness with which the naphthalene derivatives are reduced, the latter taking up as many as four atoms of hydrogen easily.

After such addition the reduced nucleus is found to have entirely lost the characteristics of a benzene nucleus, and to have become similar in properties to an alkyl radical, whereas the non-reduced nucleus assumes the character of a benzene nucleus in its entirety (*Bamberger*). (See the Tetrahydro-derivatives of the Naphthylamines and Naphthols, pp. 572 and 574.)

*Properties.*—Naphthalene crystallizes in glistening plates, is insoluble in water, sparingly soluble in cold alcohol and ligroin, but dissolves readily in hot alcohol and ether; it melts at  $80^{\circ}$  and boils at  $218^{\circ}$ . Its heat of combustion is 8614 gm. cal. It has a characteristic tarry smell, and is distinguished by the ease with which it sublimates and volatilizes with steam.

With picric acid it yields an additive compound,  $C_{10}H_8 \cdot OH \cdot C_6H_2(NO_2)_3$ , crystallizing in yellow needles and melting at  $149^{\circ}$ . It readily yields di- and tetrahydronaphthalenes,  $C_{10}H_{10}$  and  $C_{10}H_{12}$ ; both of these are liquids of pungent odour which regenerate naphthalene again when heated. By catalytic hydrogenation, the second benzene nucleus can also be made to take up hydrogen, a decahydronaphthalene, *decalin*,  $C_{10}H_{18}$ , is formed. This compound is manufactured on a large scale and is used as a turpentine substitute in the paint industry. For stereochemistry of decalin and its derivatives see Chap. L, A7. It also yields additive products with chlorine more readily than benzene does, e.g. naphthalene dichloride,  $C_{10}H_8Cl_2$ , and -tetrachloride,  $C_{10}H_8Cl_4$  (m.-pt.  $182^{\circ}$ ); the latter is oxidized to phthalic acid more easily than naphthalene itself, hence that acid is sometimes prepared from it on the large scale.

Naphthalene is principally used for the preparation of phthalic acid (for eosin, indigo, &c.), and of naphthylamines and naphthols (for azo-dyes); also for the carburation of illuminating gas. It is a powerful antiseptic also, and is used therapeutically, and for moth balls and as soil fumigant.

## B. Naphthalene Derivatives

The number of substitution products in the case of naphthalene is greater than with benzene, and on the whole they are formed more readily.

*The mono-derivatives invariably exist in two isomeric forms, the  $\alpha$ - and  $\beta$ -compounds, e.g.:  $C_{10}H_7Cl$  ( $\alpha$ - and  $\beta$ -chloro-naphthalene).  $C_{10}H_7NH_2$  ( $\alpha$ - and  $\beta$ -naphthylamine).  $C_{10}H_7OH$  ( $\alpha$ - and  $\beta$ -naphthol).  $C_{10}H_7CH_3$  ( $\alpha$ - and  $\beta$ -methyl-naphthalene).*

The existence of two series of mono-derivatives has not only been established empirically, but it has also been proved (in a manner similar to that given on p. 386 *et seq.* for benzene) that in the naphthalene molecule two sets of hydrogen atoms

(the  $\alpha$  and  $\beta$ ,  $\alpha = 1, 4, 5, 8$ ;  $\beta = 2, 3, 6, 7$ ) have an equal value as regards one another, but the atoms of the one set differ from those of the other, so that the  $\alpha$ - and the  $\beta$ -positions occur severally four times, i.e. twice in each benzene nucleus (*Atterberg*).

The above constitutional formula for naphthalene satisfies these conditions, since, according to it, the positions 1, 4, 5, and 8 are severally equal and also the positions 2, 3, 6, and 7, but not the positions 1 and 2. The conception that in the  $\alpha$ -compounds the position 1, 4, 5, or 8 is occupied is due to *Liebermann* (A., 183, 225), *Reverdin* and *Noelting* (B., 1880, 36), and *Fittig* and *Erdmann* (cf. the formation of  $\alpha$ -naphthol given above).

With regard to the di-derivatives of naphthalene, a considerable number of isomerides of many are known; according to the naphthalene formula, ten are theoretically possible in each case when the two substituents are the same, and fourteen when they are different. The ten possible isomerides are 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 2:3, 2:6, and 2:7. All other combinations are identical with one of these ten. According to *Armstrong* and *Wynne* ten dichloro- and fourteen trichloro-naphthalenes are actually known (cf. C. and I., 1934, 686).

The position 1:3 is termed the "*peri*-" position; it resembles the ortho-position to some extent, e.g. *peri*-naphthalene-dicarboxylic acid like an *o*-dicarboxylic acid yields an anhydride.

The **homologues** of naphthalene are of comparatively small importance, and are usually prepared by *Fittig's* or by *Friedel* and *Crafts'* synthesis, but the latter reaction does not proceed at all smoothly. Most of them are liquids, and on oxidation yield acids resembling benzoic acid.

**1-Chloro-naphthalene** is obtained in 85 per cent yield by chlorinating in cold benzene suspension with an iron catalyst and octachloronaphthalene is formed by prolonged chlorination in presence of iron and has m.-pt.  $198^{\circ}$ .

**1-Bromo-naphthalene**, prepared by brominating naphthalene, is partially converted into the 2-compound when heated with aluminium chloride. Its bromine atom is somewhat more readily exchangeable than that of bromo-benzene, but cannot be eliminated by boiling with alkalis. Interesting methods of formation of the chloro-derivatives are by heating

the hydroxy-, nitro-, or sulphonic acid derivatives with phosphorus pentachloride.

**1-Nitro-naphthalene**,  $C_{10}H_7 \cdot NO_2$  (*Laurent*, 1835), is formed by the direct nitration of naphthalene. It crystallizes in yellow prisms, melts at  $56.5^\circ$ , boils without decomposition, and readily yields 1 : 5 and 1 : 8 di- and various tri- and tetra-nitro-naphthalenes upon further nitration. On reduction it is converted into  $\alpha$ -naphthylamine. When subjected to catalytic oxidation with air in presence of vanadic oxide it yields phthalimide and phthalic anhydride. The position of the nitro-group has been established by conversion of the compound into  $\alpha$ -naphthol.

The isomeric  $\beta$ - or 2-nitro-naphthalene can be obtained indirectly by diazotizing  $\beta$ -naphthylamine, and acting on the product with sodium nitrite in presence of cuprous oxide (*B.*, 1887, 1494; 1903, 4157); it crystallizes in bright yellow needles melting at  $79^\circ$ .

**$\alpha$ -Naphthylamine**,  $C_{10}H_7 \cdot NH_2$  (*Zinin*), forms colourless needles or prisms, melts at  $49^\circ$ , boils at  $300^\circ$ , and is readily soluble in alcohol. It can be obtained by reducing the 1-nitro-compound, and also readily by heating  $\alpha$ -naphthol with the double compound of calcium chloride and ammonia, while aniline can only be prepared from phenol in a similar manner with difficulty:  $C_{10}H_7 \cdot OH + NH_3 = C_{10}H_7 \cdot NH_2 + H_2O$ .

It possesses a disagreeable faecal-like odour, sublimes readily, and turns brown in the air. Certain oxidizing agents, such as ferric chloride, produce a blue precipitate with solutions of its salts, while others give rise to a red oxidation product; chromic anhydride oxidizes it to  $\alpha$ -naphthaquinone. In other respects it resembles aniline. Its hydrochloride is only sparingly soluble in water.

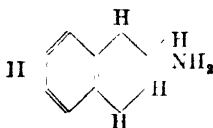
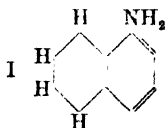
**$\beta$ -Naphthylamine**,  $C_{10}H_7 \cdot NH_2$  (*Liebermann*, 1876), is now generally prepared by passing  $\beta$ -naphthol vapour and ammonia over alumina at  $430^\circ$ – $450^\circ$ , or by the action of ammonium hydroxide and sulphite on  $\beta$ -naphthol. Naphthyl ammonium sulphite is formed as an intermediate product and reacts with the ammonia, yielding naphthylamine and ammonium sulphite. This reaction is frequently used for transforming derivatives of  $\alpha$ - and  $\beta$ -naphthol into corresponding amino-compounds. The reaction is reversible and can be used for replacing  $NH_2$  by  $OH$ .

$\beta$ -Naphthylamine crystallizes in nacreous plates, melts at

112°, boils at 294°, and has no odour. It is more stable than  $\alpha$ -naphthylamine, and is not coloured by oxidizing agents.

Both of these naphthylamines can be converted into tetrahydro-compounds by the action of sodium and amyl alcohol (i.e. nascent hydrogen). The **tetrahydro- $\alpha$ -naphthylamine** resembles its mother substance closely in most of its properties, e.g. it can be diazotized and has entirely assumed the character of aniline; the hydrogen atoms have entered the nucleus which does not contain the amino-group. It is termed *aromatic* or "*ar*"-tetrahydro- $\alpha$ -naphthylamine (Formula I). **Tetrahydro- $\beta$ -naphthylamine**, on the other hand, is not diazotized by nitrous acid, but transformed into a very stable nitrite. Here it is the benzene nucleus containing the amino-group which has become reduced; the compound has assumed the properties of an amine of the fatty series, and is termed *alicyclic* or "*ac*"-tetrahydro- $\beta$ -naphthylamine (Formula II). The  $\alpha$ -compound is oxidizable to adipic acid (p. 264), and the  $\beta$ -compound to *o*-hydrocinnamo-carboxylic

acid,  $\text{C}_6\text{H}_4 \begin{cases} \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H} \\ \text{CO}_2\text{H} \end{cases}$  (Bamberger and others, B., 1888-1890).



An *ac*-tetrahydro- $\alpha$ - and an *ar*-tetrahydro- $\beta$ -naphthylamine have also been prepared.

Both naphthylamines yield **methyl-** and **dimethyl-naphthylamines**, **phenyl- $\alpha$ -** and **- $\beta$ -naphthylamines** (which are of technical importance), **nitro-naphthylamines**, **diamino-naphthalenes** or **naphthylene-diamines**,  $\text{C}_{10}\text{H}_6(\text{NH}_2)_2$ , **diazonium-compounds** (which are in every respect analogous to the diazonium salts of benzene, especially in the formation of azo-dyes, many of which are of great technical importance), **diazo-amino-compounds**, &c.

The **diazo - amino - naphthalene**,  $\text{C}_{10}\text{H}_7\text{:N:N}\cdot\text{NH}\cdot\text{C}_{10}\text{H}_7$ , which is formed by the action of nitrous acid upon  $\alpha$ -naphthylamine, readily undergoes a molecular transformation (like the corresponding benzene compound) into **amino-azo-naphthalene**,

$C_{10}H_7 \cdot N : N \cdot C_{10}H_6 \cdot NH_2$ . This latter compound crystallizes in brownish-red needles with a green metallic lustre, and can be diazotized, its diazo-compound yielding  $\alpha$ -azo-naphthalene,  $C_{10}H_7 \cdot N : N \cdot C_{10}H_7$  (red to steel-blue glistening prisms), when boiled with alcohol. This last is not readily obtained by the methods which hold good for azo-benzene.

A mixture of naphthalene  $\alpha$ - and  $\beta$ -sulphonic acids,  $C_{10}H_7 \cdot SO_3 \cdot OH$ , is obtained by warming naphthalene to  $80^\circ$  with concentrated sulphuric acid. They may be separated by aid of their calcium or barium salts, or as aniline or *m*-toluidine salts, as the  $\beta$ -sulphonates are less soluble than the  $\alpha$ -salts. The  $\alpha$ -acid is transformed into the  $\beta$ -acid when heated with concentrated sulphuric acid, and hence the chief product obtained by sulphonating naphthalene at  $160^\circ$  is the  $\beta$ -acid (*Witt*, B., 1915, 743). At  $40^\circ$  the product contains 96 per cent of  $\alpha$  and at  $165^\circ$  85 per cent of  $\beta$  (J. S. C. I., 1923, 421T). The sulphonic acid radicals in these compounds may be more readily replaced by hydroxyl or cyanogen than in the benzene series (B., 1914, 3160).

**Naphthalene-disulphonic acids**,  $C_{10}H_6(SO_3H)_2$ .—With acid containing a little  $SO_3$  the product at  $40^\circ$  contains 75 per cent of the 1 : 5- and 25 per cent of the 1 : 6-disulphonic acid at  $40^\circ$ – $130^\circ$  the product is a mixture of 1 : 6- and 2 : 7-disulphonic acid; at  $140^\circ$  the 2 : 6-acid makes its appearance, and at  $180^\circ$  30 per cent of the product is the 2 : 6-acid.

**Naphthylamine - mono - sulphonic acids**,  $NH_2 \cdot C_{10}H_6 \cdot SO_3 \cdot OH$ .—Thirteen isomers of these are known (7  $\alpha$ - and 6  $\beta$ -). **Naphthionic acid** ( $NH_2 : SO_3H = 1 : 4$ ) is obtained by the sulphonation of  $\alpha$ -naphthylamine; it is employed in the preparation of azo-dyes, as are also several of its isomers and various naphthylamine-disulphonic acids. These last are obtained (a) directly from  $\alpha$ - or  $\beta$ -naphthylamine (*Green* and *Vakil*, J. C. S., 1918, 35), or (b) by nitrating the naphthalene-sulphonic acids and then reducing to the amine.

$\alpha$ - and  $\beta$ -Naphthols,  $C_{10}H_7 \cdot OH$ , which are present in coal-tar, can be easily prepared, not only from the naphthalene-sulphonic acids as above, but also by diazotizing the naphthylamines. They crystallize in glistening plates, have a phenolic odour, and dissolve readily in alcohol and ether but only sparingly in hot water.  $\alpha$ -Naphthol (*Griess*, 1866) melts at  $96^\circ$  and boils at  $288^\circ$ , while  $\beta$ -naphthol (*Schäffer*, 1869) melts at  $122^\circ$  and boils at  $295^\circ$ ; both are readily volatile at ordinary



temperatures. They possess a phenolic character, but nevertheless resemble the alcohols of the benzene series more than the phenols, their hydroxy-groups being much more reactive than those of the latter, e.g. they can be readily replaced by amino-groups (see above).  $\beta$ -Naphthol is an antiseptic.

**ar-Tetrahydro- $\alpha$ -naphthol**,  $C_{10}H_7H_4(OH)$ , obtained by reducing  $\alpha$ -naphthol, has the character of a pure phenol, and not that of  $\alpha$ -naphthol. A mixture of **ar-** and **ac-tetrahydro- $\beta$ -naphthols** is obtained from  $\beta$ -naphthol, the *ar*-compound corresponds with phenol and the *ac*-compound with alcohol.

Ferric chloride oxidizes  $\alpha$ - and  $\beta$ -naphthols, with production of violet and greenish colorations respectively, to **di-naphthols**,  $C_{20}H_{12}(OH)_2$ , which are derivatives of di-naphthyls (p. 576). The cautious oxidation of  $\alpha$ -naphthol yields ***o*-cinnamo-carboxylic acid**,  $CO_2H \cdot C_6H_4 \cdot CH:CH \cdot CO_2H$ , and that of  $\beta$ -naphthol, ***o*-carboxy-phenyl-glyoxylic acid**,  $CO_2H \cdot C_6H_4 \cdot CO \cdot CO_2H$ .

The naphthols yield alkyl and acyl derivatives. The ethers are formed by the action of an alcohol and hydrogen chloride on the naphthols, and in this respect the naphthols resemble acids.  **$\beta$ -Naphthyl-methyl-ether**,  $C_{10}H_7 \cdot O \cdot CH_3$ , and the corresponding ethyl and butyl ethers are the *nerolins* used as orange and strawberry odours in the perfumery industry.

From the naphthols, as from the phenols, there are derived **nitro-, dinitro-, trinitro-, and amino-compounds**, &c. The calcium salt of **dinitro- $\alpha$ -naphthol**,  $C_{10}H_5(NO_2)_2 \cdot OH$ , is known as *Martius'* yellow or naphthalene yellow, and its sulphonic acid, **naphthol yellow S** or *fast yellow*, is a valuable dye.

**Amino-naphthols**,  $C_{10}H_6(NH_2)(OH)$ , are obtained by the reduction of nitro-naphthols; like the amino-phenols they are readily oxidized in the air. ( $NH_2:OH$  in the  $\alpha$ -compound = 1 : 4, in the  $\beta$ -compound = 1 : 2.)

A number of **naphthol-mono-, di-, &c., sulphonic acids** are known, also amino-naphthol-sulphonic acids, which are of great technical value. Among these may be mentioned 1 : 4-**naphthol-sulphonic acid** (*Nevile* and *Winther*), from naphthionic acid, the 2 : 8-acid, the 2 : 6-acid, the  **$\beta$ -naphthol-disulphonic acids R** (2 : 3 : 6) or "**R-salt**", and **G** (2 : 6 : 8) or "**G-salt**". 1-Amino-8-naphthol-3 : 6-disulphonic acid = **H acid**.

**Sodium 1-amino-2-naphthol-6-sulphonate** is used as a photographic developer under the name of *Eikonogen*.

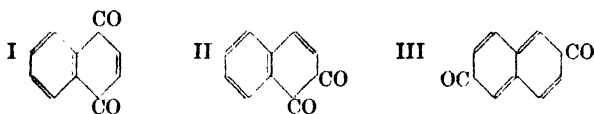
**Azo-dyes**.—A series of very important azo-dyes (see also under Benzidine, p. 543) is produced by the action of dia-

zonium compounds, and of diazo-naphthalene-sulphonic acids upon the naphthylamines and naphthols, and especially upon the sulphonic acids of these mentioned above. Some of the more important of these are described in Chap. LIX, B.

**Quinones of the Naphthalene Series.**—Three isomeric quinones,  $C_{10}H_6O_2$ , are known; two correspond with para- and ortho-benzoquinones.

**$\alpha$ -Naphthaquinone** may be obtained by the oxidation of naphthalene,  $\alpha$ -naphthylamine, 1-amino-4-naphthol, 1:4-dihydroxy-naphthalene, and of various derivatives of naphthalene containing substituents in the  $\alpha$ -positions, with chromic acid. It crystallizes in yellow rhombic plates, melts at  $125^\circ$ , and is the complete analogue of ordinary quinone, having a similar odour and being volatile with steam. It can be reduced to 1:4-dihydroxy-naphthalene by sulphurous acid, and can yield a dioxime, hence its constitution as a para- or 1:4-quinone (Formula I).

**$\beta$ -Naphthaquinone** (II) has no odour and is not volatile, being thus more like phenanthraquinone. It can be obtained by the oxidation of 1-amino-2-naphthol, and when reduced with sulphurous acid yields 1:2-dihydroxy-naphthalene; hence its constitution as a 1:2 or orthoquinone. It decomposes at  $115^\circ$  without melting and crystallizes in red needles:

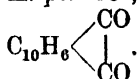


2:6-Naphthaquinone (III), isomeric with the  $\alpha$ - and  $\beta$ -compounds, forms odourless, non-volatile, yellowish-red prisms, and is a strong oxidizing agent.

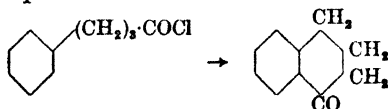
Hydroxy-naphthaquinones are known; the common one is 2-hydroxy- $\alpha$ -naphthaquinone; **juglone** is the isomeric 5-hydroxy-compound, and occurs in nut shells; **naphthazarine**, 5:8-dihydroxy- $\alpha$ -naphthaquinone, "alizarin black", is a valuable dye which is prepared by acting upon  $\alpha$ -dinitro-naphthalene with zinc and sulphuric acid, comports itself like the alizarin dyes; it is the "alizarin" of the naphthalene series. Its structure follows from its synthesis from the condensation of quinol and maleic anhydride and subsequent elimination of  $CO_2$ .



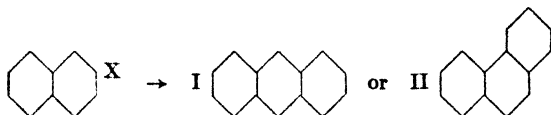
m.-pt.  $93^{\circ}$ , and when oxidized gives **acenaphthaquinone**,



The fusion of a second ring with a benzene ring can take place in one way only and the product is a naphthalene derivative, e.g.  $\text{C}_6\text{H}_5\cdot(\text{CH}_2)_3\cdot\text{COCl}$  can give only the keto form of tetrahydronaphthalene:



When, however, a third ring condenses with a naphthalene ring the fusion can take place theoretically in two different ways:



The former is termed linear and the latter angular condensation, and the products are respectively anthracene and phenanthrene derivatives. The occurrence of so many natural complex phenanthrene derivatives, e.g. resin acids, steroids, heart poisons, &c., indicates that nature favours the angular condensation.

In laboratory operations this angular condensation is frequently, but not universally, met with. Thus  $\beta$ -naphthylamine when subjected to the *Skraup* condensation gives an angular product, and similarly the acid chloride  $\beta\text{-C}_{10}\text{H}_7\cdot(\text{CH}_2)_3\cdot\text{COCl}$  yields a phenanthrene derivative. This fact has been used as an argument in favour of the symmetrical structure I (p. 568) for naphthalene rather than the unsymmetrical structure, as condensation usually takes place on to two C atoms united by an olefine bond (cf. *Pauling*, J. Chem. Phys., 1933, 365; *Waldemann*, B., 1931, 1713; *Mills*, J. C. S., 1930, 2510).

## XXXII. THE ANTHRACENE AND PHENANTHRENE GROUPS

### A. Anthracene

**Anthracene**,  $C_{14}H_{10}$  (*Dumas and Laurent*, 1832; *Fritzsche*, 1857), is formed, together with benzene and naphthalene, by the destructive distillation of coal and, generally, by the pyrogenous reactions which give rise to these products, e.g. by passing  $CH_4$ ,  $C_2H_6$ ,  $C_2H_2$ , the vapour of alcohol, &c., through red-hot tubes.

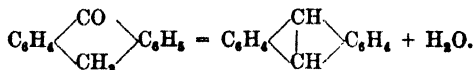
Although coal-tar contains only some 0.25–0.45 per cent of anthracene, it is the chief source from which this hydrocarbon is obtained. The fraction of coal-tar distilling above  $270^\circ$  and known as anthracene oil yields, on further distillation and digesting with solvent naphtha, a solid mass known as 50-per-cent anthracene, which is then distilled with one-third of its weight of potassium hydroxide. This serves to remove carbazole (p. 543), which yields a non-volatile potassium derivative

$\begin{array}{c} C_6H_4 \\ | \\ C_6H_4 \end{array} \rangle NK$ , and the distillate consists of anthracene

and phenanthrene. The phenanthrene is removed by extraction with carbon disulphide, and the anthracene crystallized from benzene. Heterocyclic compounds, e.g. carbazole, can also be removed by preferential oxidation of the vapours in presence of suitable catalysts.

The following are some of the more important methods by means of which the hydrocarbon has been synthesized, and they throw considerable light upon its constitution:

1. By heating *o*-tolyl phenyl ketone with zinc dust (*Elbs.*, 1874), or passing over activated charcoal (1925):

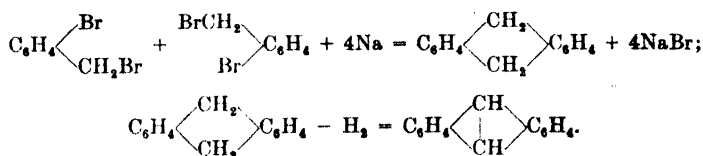


2. Together with dibenzyl, by heating benzyl chloride with water at  $200^\circ$  (1874):

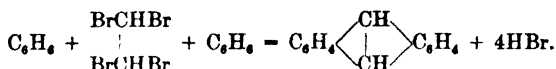


3. From *o*-bromo-benzyl bromide and sodium in ethereal solution, dihydro-anthracene is at first formed, and this is

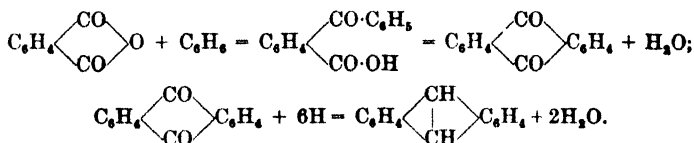
converted by oxidation (which is partly spontaneous during the above reaction) into anthracene (B., 1879, 1965):



4. By heating benzene with symmetrical tetrabromo-ethane and aluminium chloride (*Anschütz*, B., 1883, 623):



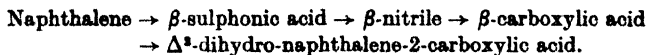
5. When phthalic anhydride is heated with benzene and aluminium chloride, *o*-benzoyl-benzoic acid is formed, and this when heated with phosphoric anhydride yields anthraquinone (*Behr* and *v. Dorp*), which on reduction with zinc dust gives anthracene:



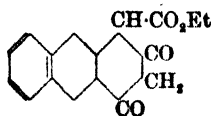
6. A mixture of *m*-xylene and styrene, treated with concentrated sulphuric acid, yields *α*-tolyl-*β*-phenyl-propane,

$\text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH} \begin{array}{c} \text{C}_6\text{H}_5 \\ \diagup \\ \text{CH}_3 \end{array}$ , which decomposes almost quantitatively into methane, hydrogen, and methyl-anthracene when strongly heated (B., 1890, 3272).

7. An interesting synthesis from naphthalene is the following:

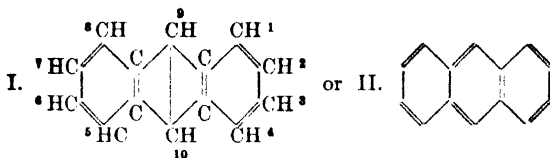


The ethyl ester of this condenses with ethyl aceto-acetate, giving



which on hydrolysis, elimination of  $\text{CO}_2$ , and distillation with zinc dust gives anthracene (J. A. C. S., 1921, 898).

*Constitution.*—From mode of formation 5, the anthracene molecule is seen to contain two benzene nuclei,  $\text{C}_6\text{H}_4$ , joined together by a middle group,  $\text{C}_2\text{H}_2$ . The carbon atoms of this middle group are likewise linked together, as is seen from mode of formation 4, and take up the *o*-position with regard to each other on one or other of the benzene nuclei (on one nucleus according to methods of formation 1 and 5, and on the other according to method 3; for further proofs of this see, e.g., v. Pechmann, B., 1879, 2124). The structure of anthracene is thus (Graebe and Liebermann):

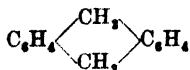


The two carbon atoms of the middle group thus form a new hexagon-ring with the carbon atoms of the benzene nuclei to which they are linked, so that anthracene may also be looked upon as being built up by the condensation of 3 six-membered carbon rings. All three rings are not true benzene rings.

The "quinonoid" formula II,  $\text{C}_6\text{H}_4 \begin{array}{c} \text{CH} \\ \diagup \quad \diagdown \\ \text{CH} \end{array} \text{C}_6\text{H}_4$  has also to be taken into consideration (Armstrong, P., 1890, 101; Kehrman, B., 1894, 3348).

*Properties and Behaviour.*—Anthracene crystallizes in colourless plates with a magnificent blue fluorescence. It is insoluble in water and dissolves only sparingly in alcohol and ether, but readily in hot benzene. It melts at  $218^\circ$ , boils at  $342^\circ$ , and with picric acid yields an additive compound which crystallizes in beautiful red needles melting at  $138^\circ$ .

Anthracene is transformed by sunlight into the polymeric *para*-anthracene,  $(\text{C}_{14}\text{H}_{10})_2$ . When hydrogenated under pressure it yields 9 : 10-dihydro-anthracene,

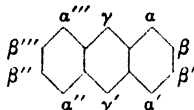


(see p. 579, mode of formation 3). This crystallizes in colour-

less plates, melts at  $107^{\circ}$ , and is readily soluble in alcohol. It sublimes readily and distils without decomposition, but yields anthracene at a red heat or when warmed with concentrated sulphuric acid. When further hydrogenated it forms 1 : 2 : 3 : 4-tetrahydroanthracene, and finally 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydroanthracene, leaving the central ring a true benzene ring (alternate single and double bonds; B., 1924, 2003; 1925, 2667).

### DERIVATIVES OF ANTHRACENE

Theoretically three isomeric mono-derivatives are possible in each case, viz. the  $\alpha$ -,  $\beta$ -, and  $\gamma$ -compounds:



since in the graphical formula given on the preceding page,  $1 = 4 = 5 = 8 = \alpha$ ,  $2 = 3 = 6 = 7 = \beta$ , and  $9 = 10 = \gamma$ . The observed facts are in complete accordance with this.

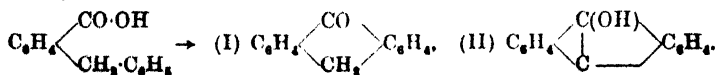
The position of the substituting group can usually be determined either by an examination of the oxidation products, e.g. if it be in the  $\gamma$ -position it will be eliminated and anthraquinone formed; or it is arrived at from the synthesis of the compound, e.g. in the case of alizarin, the formation of which from catechol and phthalic acid shows that its two hydroxyls are contained in one and the same benzene nucleus.

The number of di-substituted derivatives is large, for example, when both substituents are alike, 15 isomerides are theoretically possible.

Numerous derivatives of anthracene are known, e.g. halogen-, nitro-, amino-, and sulphonic acid derivatives.

**Hydroxy-anthracenes.**—The  $\alpha$ - and  $\beta$ -compounds are termed 1- and 2-anthrols; they are obtained by fusing the corresponding sulphonic acids with alkali, and in their properties closely resemble phenols and naphthols.

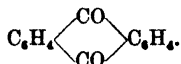
**9-Hydroxy-anthracene** or **anthranol** may be obtained by reducing anthraquinone with zinc and acetic acid, or synthetically, by the action of concentrated sulphuric acid on *o*-benzyl-benzoic acid at  $80^{\circ}$ :



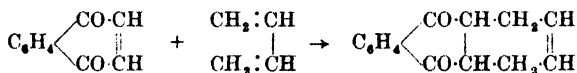


It is a typical tautomeric substance, in pyridine it has the hydroxy-anthracene structure II, but the solid has the ketonic structure I, and is readily oxidized to anthraquinone.

**Anthraquinone**,  $C_{14}H_8O_2$  (*Laurent*, 1834), is readily obtained by oxidizing anthracene with chromic acid mixture, or on the large scale by atmospheric oxidation at  $180^{\circ}$ – $280^{\circ}$  in presence of catalysts, e.g. vanadates, chromates or molybdenates of Ag, Pb, Ni and Co:



Two synthetical methods of formation are: (1) From phthalic anhydride to *o*-benzoyl-benzoic acid (Chap. XXVIII), a process now used industrially. (2) The diene synthesis from  $\alpha$ -naphthaquinone and butadiene (Chap. LI, C3) in alcoholic solution at  $100^{\circ}$  under pressure; the product tetrahydroanthraquinone is readily oxidized by air or  $CrO_3$  to anthraquinone:



It crystallizes in yellow prisms or needles soluble in hot benzene, melts at  $285^{\circ}$ , sublimes with great readiness, and is exceedingly stable as regards oxidizing agents. Hydriodic acid at  $150^{\circ}$  reduces it either to anthracene or its dihydride, while fusion with potash converts it into benzoic acid. It possesses more of a ketonic than of a quinone character (*Zincke, Fittig*), as it is not reduced by sulphurous acid, and gives an oxime with hydroxylamine.

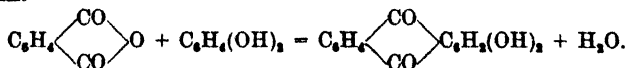
Numerous substituted anthraquinones are known. Nitric acid attacks the 9:10-positions forming additive compounds. Anthraquinone with concentrated sulphuric acid at  $260^{\circ}$  or with oleum at lower temperatures yields the 2-sulphonic acid, but at higher temperatures both yield the 2:6- and 2:7-disulphonic acids. The addition of 2 per cent of mercuric salt to the acid or oleum leads to the formation of the 1-mono- and 1:5-di- and 1:8-di-sulphonic acids.

In anthraquinone derivatives the substituents display marked mobility, nearly all 1-nitroanthraquinones yield the 1-sulphonic acids when heated with an aqueous solution of sodium sulphite, and thus the 1-nitroanthraquinone-6 or 7-sulphonic yield the 1:6- or 1:7-disulphonates. On the whole,

the 2-substituted compounds are more stable than the 1-isomerides. The 1-halogenated compounds behave in the same manner and the 1-sulphonic acid with sodium chlorate yields the 1-chloro-compound and the 1:5-disulphonic acid yields 1:5-dichloroanthraquinone. If a sulphonic acid is heated with 80 per cent sulphuric acid in the presence of mercury or formic acid the  $\text{SO}_3\text{H}$  group is replaced by H (*Fierz-David*, *Helv.*, 1927, 225). The  $\text{SO}_3\text{H}$  group in position 1 or 2 is readily replaced by  $\text{NH}_2$  or  $\text{NHR}$  on heating the acid with ammonia or an amine under pressure, and 2-aminoanthraquinone, an intermediate for the manufacture of indanthrone (*Chap. LIX*, K2), is made by this method. The  $\text{SO}_3\text{H}$ , Cl or  $\text{NO}_2$  groups are readily replaced by OEt or OPh by heating with NaOEt or NaOPh at  $200^\circ$ , and OH in position 1 can be replaced by  $\text{NH}_2$  by heating with aqueous ammonia. Hydroxy-compounds are readily formed by heating sulphonic acids with milk of lime at  $180^\circ$ – $200^\circ$  under pressure and no further oxidation to dihydroxy-anthraquinones occurs.

Fusion of the sulphonic acids with potash does not generally yield the analogous hydroxy-compounds in theoretical quantity, oxygen being usually absorbed from the air at the same time; thus the mono-sulphonic acids yield mono- and dihydroxy-, and the di-sulphonic acids di- and trihydroxy-anthraquinones. In practical working the theoretical amount of chlorate of potash required is added to the "melt". Prolonged fusion with potash tends to form hydroxy-benzoic acids.

**Hydroxy-anthraquinones** can also be prepared by the synthetical mode of formation 5, p. 579, viz. from phthalic anhydride and the mono- or dihydroxy-benzenes (*Baeyer and Caro*), e.g. phenol yields 1- and 2-hydroxy-anthraquinones (yellow needles), catechol yields alizarin, quinol yields quinizarin.



The hydroxy-derivatives are also produced by fusing chloro- and bromo-anthraquinones with potash, while *m*-hydroxybenzoic acid can be converted directly by sulphuric acid into anthraflavic acid, water being eliminated.

Hydroxy-anthraquinones are also formed by the action of concentrated sulphuric acid or oleum under pressure and with a Se or Hg compound as catalyst and hydrolysing the sul-

phuric acid esters so formed. As many as 6 OH groups can be thus introduced, viz. 1 : 2 : 4 : 5 : 6 : 8 and 1 : 2 : 4 : 5 : 7 : 8.

The following are the various hydroxy-anthraquinones and the names under which they are commonly known:

1 = Erythroanthraquinone, 1 : 2 = alizarin, 1 : 3 = xanthopurpurin, 1 : 4 = quinizarin, 1 : 5 = anthrarufin, 1 : 8 = chrysazin, 2 : 3 = hystazarin, 2 : 6 = anthraflavin, 2 : 7 = isoanthraflavin, 1 : 2 : 3 = anthragallol, 1 : 2 : 4 = purpurin, 1 : 2 : 6 = flavopurpurin, 1 : 2 : 7 = anthrapurpurin, 1 : 2 : 8 = hydroxy-chrysazin, 1 : 2 : 5 : 6 = rufiopin, 1 : 2 : 5 : 8 = quin-alizarin or alizarin bordeaux, 1 : 3 : 5 : 7 = anthrachrysin, 1 : 2 : 4 : 5 : 8 = alizarin cyanin R, 1 : 2 : 3 : 5 : 6 : 7 = rufigallol, 1 : 2 : 4 : 5 : 6 : 8 = anthracene blue, 1 : 2 : 4 : 5 : 7 : 8 = alizarin hexacyanin.

In many cases the actual commercial products are mixtures of several compounds.

The common method of formation is by fusion of a sulphonic acid with the necessary amount of chlorate to give one more OH group than the number of  $\text{SO}_3\text{H}$  groups present. During fusion with potash rearrangement can occur, thus phthalic anhydride and *o*-dichlorobenzene with  $\text{AlCl}_3$  yield 2 : 3-dichloroanthraquinone, but on alkali fusion this gives alizarin the 1 : 2-dihydroxy-compound (J. A. C. S., 1927, 473), and the same product is formed on fusing 2-chloro-3-hydroxy-anthraquinone with alkali.

OH groups in position 2 are readily methylated by methyl iodide or sulphate and alkali, whereas the same group in position 1 is much less active, and for methylation diazomethane must be used; this may be due to chelation of OH and CO (cf. Chap. XLVI, B. and C.). The carbonyl group is not so readily reduced to  $>\text{CH}\cdot\text{OH}$  when an OH group is present in position 1.

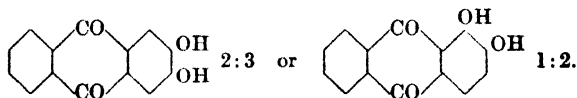
**Alizarin**, 1 : 2-dihydroxy-anthraquinone,  $\text{C}_{14}\text{H}_8\text{O}_4$ , is the most important constituent of the ancient beautiful red dye of the madder root (*Rubia tinctorum*), and is present as the glucoside, Ruberythric acid,  $\text{C}_{26}\text{H}_{28}\text{O}_{14}$ ; in addition to alizarin, madder also contains purpurin.

It crystallizes in magnificent red prisms or needles of a glassy lustre, melts at  $289^\circ$ , and can be sublimed; it dissolves readily in alcohol and ether, only sparingly in hot water, but, as a phenol, very readily in alkalis to a violet-red solution. It yields insoluble coloured compounds—the so-called “lakes”

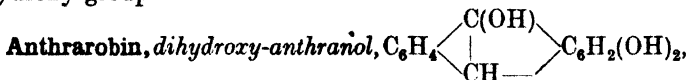
—with metallic oxides (cf. Chap. XLVI, B.), the alumina and tin lakes being of a magnificent red colour, iron lake violet-black, and lime lake blue. In the Turkey Red manufacture, for instance, the materials to be dyed are previously mordanted with acetate of alumina or with "ricinoleic-sulphuric acid".

Its constitutional formula is based on the following considerations: (a) Its conversion into anthracene when heated with zinc dust (*Graebe and Liebermann*); (b) its formation by fusing dibromo-anthraquinone or anthraquinone-sulphonic acid with potash; (c) its synthesis from phthalic anhydride and catechol.

All these indicate that it is a dihydroxy-anthraquinone with the two hydroxy-groups in the *o*-positions with respect to one another:



The fact that two isomeric mono-nitro-derivatives (with the nitro-group in the same nucleus as the two hydroxy-groups) have been prepared is a proof of the positions 1:2 for the hydroxy-groups.



obtained from alizarin, ammonia, and zinc dust, is a yellowish-white powder which yields alizarin on oxidation; on account of its reducing properties it is used in skin diseases.

Nitric peroxide converts alizarin into  $\beta$ -nitro-alizarin or alizarin orange,  $C_{14}H_7(NO_2)O_4$ , a yellowish-red dye; and this with glycerol and sulphuric acid (the *Skraup* reaction, Chap. XLIV, A2) yields **alizarin blue**,  $C_{17}H_9NO_4$  (see Quinoline), a valuable blue dye which is converted by fuming sulphuric acid into **alizarin green**.

For other examples of alizarin dyes see Chap. LIX, K2.

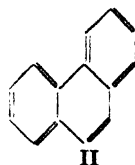
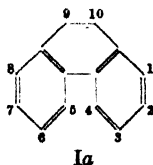
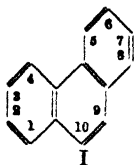
It is essential for mordant dyeing properties that two ortho OH groups should be present (*Kostanecki*).

## B. Phenanthrene

**Phenanthrene** (*Fittig* and *Ostermeyer*, 1872), isomeric with anthracene, is present in the anthracene oil fractions from coal-tar. It crystallizes in colourless, glistening plates, dissolves in alcohol more readily than anthracene, yielding a blue fluorescent solution, melts at  $99^{\circ}$ , and boils at  $340^{\circ}$ . It cannot be completely separated from anthracene, carbazole and fluorene as it forms mixed crystals with these compounds with melting-points higher than that of pure phenanthrene.

It is best separated by partial oxidation and subsequent distillation, as anthracene is more readily oxidized. Its *picrate* crystallizes in yellow needles, m.-pt.  $145^{\circ}$ , and it forms a coloured compound with trinitrobenzene melting at  $158^{\circ}$ .

It is usually represented by the structural formula I, as each ring has a benzenoid structure, whereas II and other formulæ have one ring with a non-benzenoid structure:



In all polynuclear compounds the tendency is for all rings to assume, as far as possible, the condition of an isolated benzene ring (*Fries, Walter and Schilling*, A., 1935, 516, 248).

The formula is frequently written as in Ia, which is the same as I.

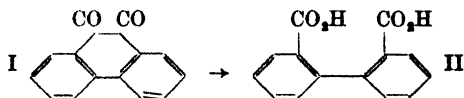
Phenanthrene is more reactive than naphthalene, but less reactive than anthracene as shown both on oxidation to a quinone and also on reduction. It has a lower energy content than anthracene, e.g. 7.0 kilo cal. The double bond in position 9:10 is the seat of reactivity; this linkage closely resembles an ordinary olefinic linkage. The dibromide is the 9:10 dibromide, the quinone is an ortho-quinone with carbonyls in these two positions. The dibromide when heated loses hydrogen bromide, yielding 9-bromo-phenanthrene. The addition of bromine is a balanced reaction and proceeds without the aid of a catalyst. (For kinetics of bromination see *Price*, J. A. C. S., 1936, 1834; *Chem. Rev.*, 1941, 137.) Five mono-

substituted,  $C_{14}H_9X$ , and twenty-six disubstituted derivatives,  $C_{14}H_8X_2$ , are theoretically possible. As a rule substitution does not occur in the 4-position.

The 2- and 3-amino-compounds are obtained from 2- and 3-acetylphenanthrenes by conversion into oximes, *Beckmann* rearrangement to acetylaminophenanthrenes and subsequent hydrolysis (J. A. C. S., 1936, 857, 2097).

When hydrogenated under pressure it yields progressively 9 : 10-dihydro-1 : 2 : 3 : 4-tetrahydro- and 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8 octahydro-derivatives. The formation of the tetra- from the di-hydro-compound is accompanied by the shifting of double links and in the octa-compound the middle ring is of the aromatic type whereas the two end rings are completely reduced (cf. Anthracene). Of the 3 compounds only the tetrahydro with an intact naphthalene nucleus forms a stable picrate.

The hydrocarbon is readily oxidized by chromic acid to phenanthraquinone I,  $C_{14}H_8O_2$ , and finally to diphenic acid,



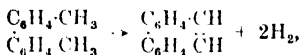
diphenyl-2 : 2'-dicarboxylic acid II (Chap. XXVII). The quinone crystallizes in yellow needles, melts at  $200^\circ$ , distils unchanged, and is not volatile with steam. It possesses the characteristics of ketones reacting with hydroxyl-amine and with sodium bi-sulphite, but is reduced to the quinol, 9 : 10-dihydroxy-phenanthrene, by sulphurous acid. It gives a bluish-green coloration with toluene containing thiotoluene, glacial acetic and sulphuric acid, and when the mixture is diluted and extracted with ether yields a violet coloured ethereal extract (*Laubenheimer* reaction).

### Syntheses of Phenanthrene and its Derivatives

Some of these syntheses are of value in deducing the structure of the hydrocarbon, and others are of value as indicating the position of the substituents in certain derivatives formed

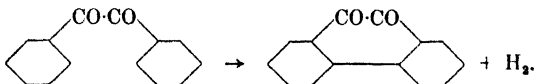
by the degradation of natural products (cf. Chap. LVII, F., and LXII).

1. Phenanthrene is formed by leading the vapours of toluene, stilbene, dibenzyl or *o*-ditolyl through a red-hot tube:

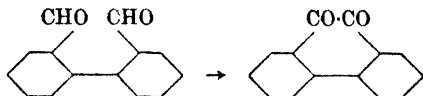


from *o*-ditolyl and sulphur, or, together with anthracene, from *o*-bromo-benzyl bromide and sodium.

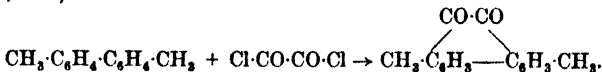
2. Phenanthraquinone (25 per cent yield) is obtained by heating benzil with aluminium chloride at 120° (Scholl and Schwarzer, B., 1922, 324).



3. Mayer (B., 1912, 1105; 1914, 406) obtained the quinone by the action of alcoholic potassium cyanide on diphenyl *o*-*o*'-dialdehyde. Probably benzoin condensation (Chap. XXV, B.) occurs followed by oxidation.



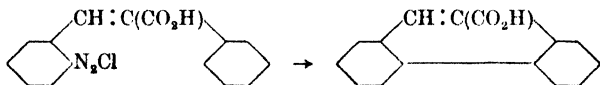
4. Alkylated phenanthraquinones are formed by the action of oxalyl chloride on alkylated diphenyls in the presence of aluminium chloride (Liebermann, B., 1911, 1453; 1912, 1186; 1913, 198).



5. 9-Hydroxy-phenanthrene is formed from diphenyl-2-acetic acid,  $\text{C}_6\text{H}_5\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , the ketone first formed yielding the tautomeric hydroxy compound (J. A. C. S., 1938, 2947).

6. **Pschorr Synthesis** (B., 1896, 496; 1900, 162, 176, 1810).—By condensing an *ortho* nitrated benzaldehyde with sodium phenylacetate (Perkin Synthesis, p. 511), the oxygen of the aldehyde eliminates water with the  $\text{H}_2$  of the methylene group, yielding, e.g.,  $\alpha$ -phenyl-*o*-nitrocinnamic acid,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot$

CH:CH:CPh·CO<sub>2</sub>H. When this is reduced, diazotized and treated with copper powder, phenanthrene-9-carboxylic acid is formed, and this on loss of carbon dioxide gives phenanthrene.

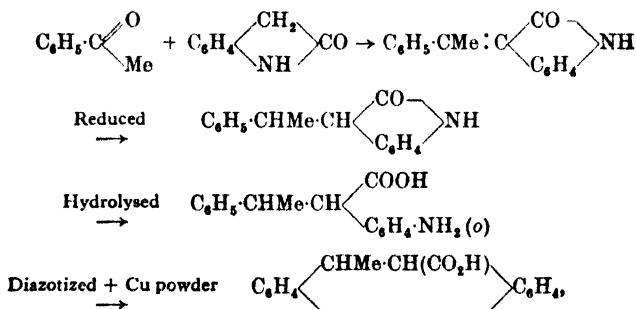


The method is of very general application and various substituted *o*-nitrobenzaldehydes and substituted phenylacetic acids can be used.

Thus with *vic.* *o*-nitrovanillin dimethyl ether, CHO·C<sub>6</sub>H<sub>3</sub>(OMe)<sub>2</sub>·NO<sub>2</sub>, and sodium phenylacetate 3:4-dimethoxy-phenanthrene-9-carboxylic acid is formed, and this on elimination of carbon dioxide yields the dimethyl ether of morphol, and is thus of aid in establishing the structure of morphine (Chap. LVIII, G.).

Windaus (B., 1924, 1871, 1875) has modified the above synthesis by using oxindole in place of phenylacetic acid and certain ketones in place of substituted benzaldehydes.

Thus with acetophenone and oxindole,

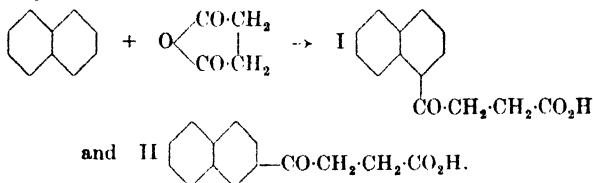


the final product is 9-methyl-9:10-dihydrophenanthrene-10-carboxylic acid.

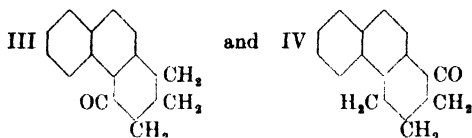
**7. Haworth Synthesis.**—Haworth and his co-workers have introduced a valuable general method for synthesizing phenanthrene derivatives. A naphthalene compound is condensed with succinic anhydride or a similar anhydride using aluminium chloride as condensing agent. Usually a mixture of



1- and 2-naphthalene- $\gamma$ -ketonic acids is formed, and these can be separated.



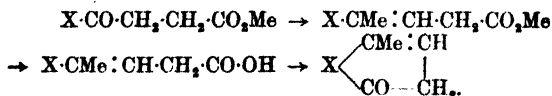
The ketonic groups are reduced by *Clemensen's* method to  $\text{CH}_2$  and then under the influence of 85 per cent sulphuric acid cyclization occurs, and in both cases a 3-ring ketone is formed, viz.:



If sulphonation should occur instead of cyclization, then the acid chloride is formed and ring closure effected by means of aluminium chloride.

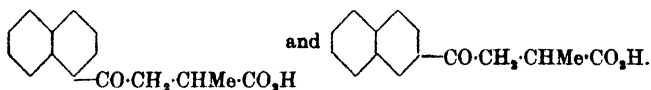
The cyclic ketones III and IV can react with *Grignard* reagents yielding secondary alcohols, which, by the elimination of water, yield respectively 4-alkylated-1:2-dihydrophenanthrenes and 1-alkylated-3:4-dihydrophenanthrenes, which can be dehydrogenated to the corresponding alkylated-phenanthrenes.

1- and 4-alkylated derivatives can also be obtained by the action of *Grignard* compounds on the esters of the ketonic acids I and II. The ketonic group reacts, the alcohol loses water giving an unsaturated ester, and the corresponding acid with sulphuric acid forms a third ring; in the case of acid II the product is a 1-alkyl derivative of keto-dihydrophenanthrene, but with I a mixture of 1- and 4-alkyl derivatives is obtained owing to migration of alkyl.



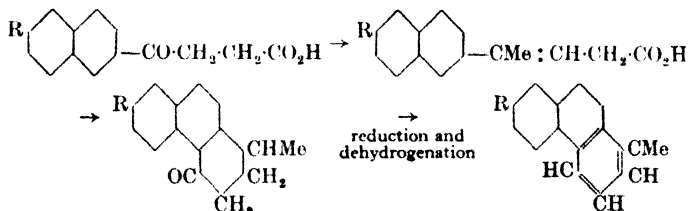
The carbonyl group in the ring can then be treated with *Grignard* reagent, and thus a 1:4-dialkylated derivative obtained.

When methyl-succinic anhydride is used the condensation with the naphthalene occurs in such a manner that the carbonyl which becomes attached to the aromatic ring is the one further removed from the methyl group, e.g.:



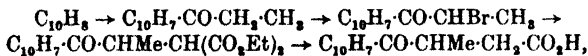
Then on reduction, cyclization and treatment with *Grignard* reagents 1 : 2 and 3 : 4 dialkyl derivatives can be obtained.

The method can be extended by starting with a naphthalene derivative containing an alkyl group; when this is in the 2-position then the condensation with the anhydride takes place in the 2nd-ring in the 6-position. Thus from 2-methyl- and 2-isopropyl-naphthalene the hydrocarbons pimanthrene (1 : 7-dimethylphenanthrene) and retene (1-methyl-7-isopropylphenanthrene) have been synthesized:

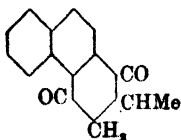


where R = Me or  $\cdot\text{CHMe}_2$ .

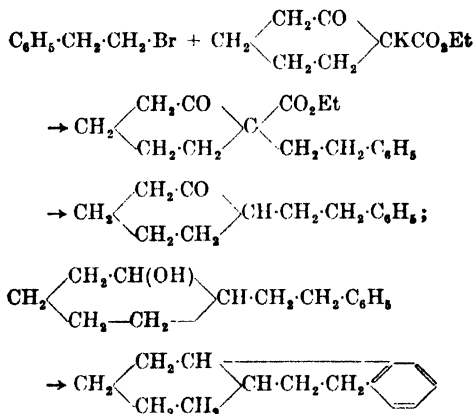
A modification of *Haworth's* synthesis consists in condensing naphthalene or one of its derivatives with an acyl bromide (*Friedel-Crafts* reaction). Brominating the resulting ketone and condensing the bromo-derivative with ethyl sodio-malonate:



hydrolysing the ester to the mono-basic acid and bringing about ring closure:

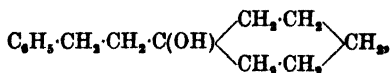


8. **Bardhan-Sen Gupta Synthesis** (J. C. S., 1932, 2520, 2798). — $\beta$ -phenylethyl bromide is condensed with the potassium derivative of ethyl cyclohexanone-2-carboxylate, alkaline hydrolysis gives not only the corresponding acid but eliminates carbon dioxide, and the resulting ketone reduced with sodium and moist ether gives the secondary alcohol which on heating with phosphorus pentoxide under reduced pressure form an unsaturated hydrocarbon which on ring closure gives an octahydrophenanthrene, and this on dehydrogenation gives phenanthrene:



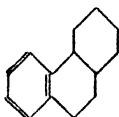
This method is also of general application and by using substituted starting materials various phenanthrene derivatives, including retene, may be obtained, and by using  $\beta$ -1-naphthyl-ethyl bromide a hydrochrysene ester can be formed (4-ring system).

9. **Bogert** (J. A. C. S., 1934, 185, 959; 1935, 151; J. Org., 1936, 288) uses a somewhat similar method, viz. condensing  $\beta$ -phenylethyl magnesium bromide,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{MgBr}$ , with cyclohexanone giving the tertiary alcohol:



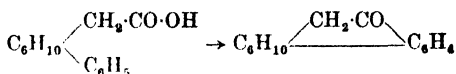
which forms a ring under the influence of concentrated sulphuric

acid giving first an unsaturated hydrocarbon and then an octahydrophenanthrene.\*



This method is also of very general application. Cook has used aluminium chloride with carbon disulphide as the ring-forming agent.

10. Cook and others (J. C. S., 1936, 71) have obtained *cis*- and *trans*- hexahydrophenanthrenes from *cis*- and *trans*-2-phenyl-cyclohexyl acetic acids:



(cf. Short and others, *ibid.* 1937).

### Resin Acids †

The common resin acids have been shown within recent years to be phenanthrene derivatives.

Many organic compounds, certain terpenes in particular, possess the property of becoming *resinified* in contact with air or under the influence of chemical reagents and then resemble the natural resins. These latter are amorphous vitreous masses, they are brittle, break with a conchoidal fracture, and are insoluble in water or acids but dissolve in alcohol, ether, terpenes, &c. They frequently occur dissolved in terpenes in the form of *oleo-resins* or *balsams*, from which they can be obtained by removal of the terpenes by steam distillation. They dissolve in alkalis forming resin soaps from which they are precipitated on the addition of acid. They are mixtures of acids or acid anhydrides. The actual compounds present in the resin in most cases are extremely unstable, so that the acids frequently isolated are not the compounds actually present but isomerides or decomposition products. The commonest resin is **rosin** or **colophonium**, the residue left after the removal of turpentine from the exudation of many species

\* A by-product is the *Spiro* compound (*J. Org.*, 1936, 288).

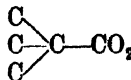
† *Chemistry of Natural Resins, Zeit.*, 1934, 58, 749.

of *Pinus*. In 1933 the amount produced was estimated at 600,000 tons. It is largely used as a size for paper (38 per cent), for the manufacture of yellow laundry soap (28 per cent), and its esters in the varnish industry as plasticizer and softener for nitro-cellulose lacquers (21 per cent). It is used as a flux in soldering and for rosening violin bows. The manganese and cobalt resins are used as driers in the paint and varnish industry.

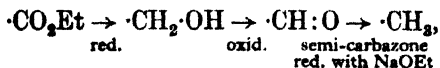
**Abietic acid**,  $C_{19}H_{29}CO_2H$ , is the chief acid obtained from common rosin. It is not an original constituent of the true secretion, and is not present to an appreciable extent in rosin, but is formed during the preparation and treatment of the rosin. Several acids isomeric with abietic acid appear to be present in the oleo-resins, but they are so extremely labile that on gently warming or contact with hydrochloric acid they yield abietic acid. For preparation cf. *Steele* (J. A. C. S., 1922, 1333; 1934, 1935). It crystallizes in small plates, melts at  $159^{\circ}$ – $161^{\circ}$ , has  $[\alpha]_D - 77^{\circ}$ , is soluble in hot alcohol, and yields a sparingly soluble acid sodium salt.

The acid itself is somewhat unstable and when heated at  $300^{\circ}$  or heated with hydrochloric or acetic acid yields an isomeric acid which still contains two olefine bonds.

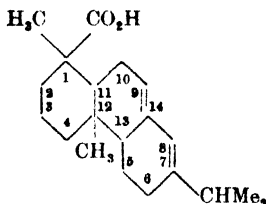
Its close relationship to retene, 1-methyl-7-*iso*-propyl-phenanthrene (p. 591) is proved by its decomposition at  $300^{\circ}$ – $330^{\circ}$  in the presence of palladinized charcoal to retene (90 per cent), hydrogen (4 mols.), methane (1 mol.) and carbon dioxide. The presence of 2 olefine links is proved by the formation of additive compounds with 2H, 4H, 2OH, 4OH, 2HBr, and that these are probably not conjugated from the fact that the formation of an additive compound with maleic anhydride does not take place below  $130^{\circ}$ , when the same additive compound is formed as that obtained from levopimaric acid, and also from its molecular refraction (B., 1936, 2193). The acid is not easily esterified and hence presumably contains the

  $CO_2H$  grouping, which also agrees with the readiness

with which carbon dioxide is eliminated. The  $CO_2H$  can be replaced by  $CH_3$  by the following stages:



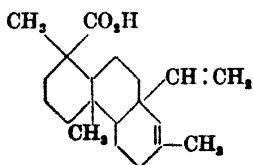
and the hydrocarbon hydrogenated loses two methyl groups yielding retene, thus indicating that both are in the form



The accompanying formula was suggested by *Ruzicka*, viz. 1 : 12-dimethyl-7-*iso*-propyl-decahydro-phenanthrene-1-carboxylic acid.

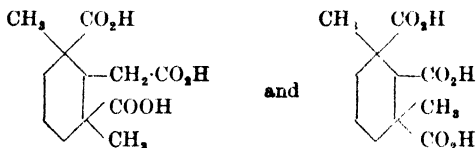
**Levopimaric acid**, present in the fresh oleo-resin, is tricyclic, has two double bonds conjugate and in the same ring, and readily yields additive compounds at the ordinary temperature with maleic anhydride, and benzoquinone, and has a structure similar to abietic acid but with double bonds in 7 : 8- and 13 : 14-positions, and the maleic anhydride compound from this acid and from abietic acid has the double bond in the 8 : 14-position.

**d-Pimaric acid**,  $\text{C}_{19}\text{H}_{29}\cdot\text{CO}_2\text{H}$ , an acid obtained from French Galipot (mainly from *Pinus maritima*), has m.-pt.  $211^\circ$  and  $[\alpha]_D + 75^\circ$  and is relatively stable to heat and to mineral acids. When the corresponding hydrocarbon is dehydrogenated it yields pimanthrene, 1 : 7-dimethylphenanthrene, the structure of which has been proved by its oxidation with potassium ferricyanide to phenanthrene-1 : 7-dicarboxylic acid and also by its synthesis by *Haworth's* method (p. 589). On ozonolysis it yields formaldehyde as one product and hence contains the vinyl group  $\cdot\text{CH}:\text{CH}_2$ . Its structural formula is represented as 1 : 7 : 12-trimethyl-14-vinyl-dodecahydro-phenanthrene-1-carboxylic acid:



The 1- and 7-positions of two methyls follow from its relationship to 1:7-dimethylphenanthrene. As the vinyl and the third methyl are removed on dehydrogenation they are quaternary groups, as is also the carboxylic group.

The structure of the left-hand ring of the two resin acids follows from the fact that when oxidized with nitric acid or permanganate both abietic and pimaric acids yield progressively the two monocyclic acids:

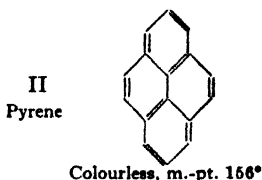
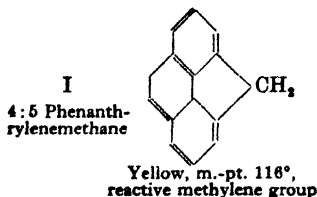


the former with 2 carboxylic groups difficult to esterify and the latter with all 3 difficult to esterify.

### C. Polynuclear Hydrocarbons\*

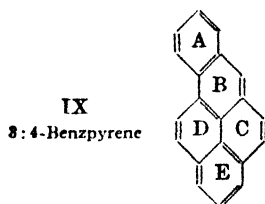
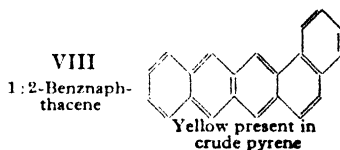
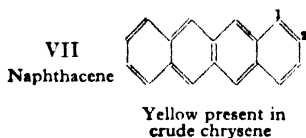
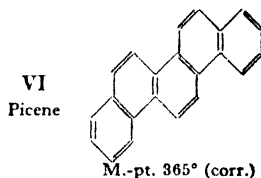
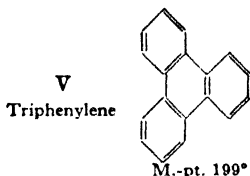
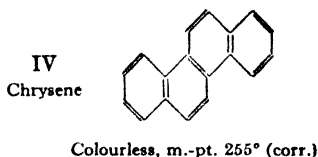
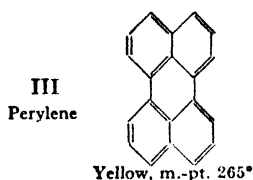
#### HYDROCARBONS FROM COAL-TAR†

Coal-tar contains many hydrocarbons of a more complex nature than anthracene and phenanthrene. Formulæ I to IX give the structures of some of the more interesting of these. Some have been known for some years, but perylene, III, and benzpyrene, IX, were isolated from tar in 1933, I in 1934, and triphenylene, V, in 1935. Several, however, viz. I, III and V, were synthesized before isolation from tar.



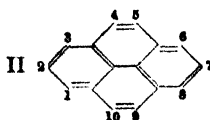
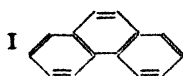
\* *Chemistry of Natural Products related to Phenanthrene*, 2nd Edition, Fieser, New York, 1937.

† Everest, *The Higher Coal-tar Hydrocarbons*, London, 1927.



IV, V and VI are formed entirely of true benzenoid rings and are relatively stable resembling naphthalene, the remainder are more reactive than phenanthrene, e.g. more readily oxidized, and are characterized by the fact that all rings are not true benzenoid rings, but contain rings with two ortho-quinonoid rings. (For discussion on structure of these hydrocarbons cf. *Kon Rep.*, 1932, 163.)

Pyrene (II), although somewhat resembling phenanthrene (I) in structure, differs in its chemical properties; when oxidized it gives a hetero-1:6-quinone, and when reduced with sodium



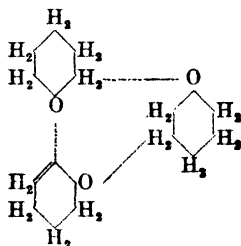


and amyl alcohol gives a sym. 1:2:3:6:7:8-hexahydro-derivative. 1:2-Benzpyrene exists in only minute quantities in coal-tar, approximately 0.0003 per cent, and is best purified by means of its picrate. It is an interesting compound as it combines within itself the ring system of 1:2-benzanthracene (ABCD) of chrysene (ABED) and of pyrene (BCDE).

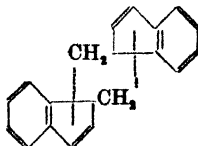
The following syntheses are of interest:

1. Perylene derivatives by the action of aluminium chloride on 1:1'-dinaphthyl compounds producing ring closure in 8:8'-positions (B., 1910, 2202).

2. Triphenylene in the form of its decahydro-derivative is obtained by the condensation of 3 mols. of *cyclohexanone* under the influence of methyl alcoholic sulphuric acid. Compare formation of mesitylene from acetone:



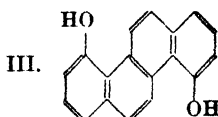
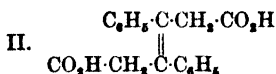
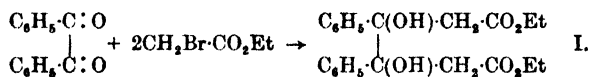
3. Chrysene. A 60 per cent yield of chrysene is obtained by passing indene through a glowing iron tube (*Spilker*, B., 1893, 1538). Rupture of the 5-membered rings in 2 molecules of indene occurs at the dotted position followed by the fusion of the two residues.



4. Picene VI is obtained by heating *s*-dinaphthyl-methane with  $\text{AlCl}_3$  and  $\text{CS}_2$  (Helv., 1934, 470).

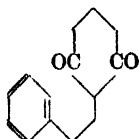
5. As already pointed out (cf. alizarin and anthraquinone) cyclic ketones can be formed by the elimination of water from certain aromatic acids such as *o*-benzoyl benzoic or  $\gamma$ -phenylbutyric acids or of hydrogen chloride from their acid chlorides, and this method has been extended to the formation of 4-ring

systems. Thus benzil and ethyl  $\alpha$ -bromo-acetate yield by the *Reformatsky* reaction the ester I which on dehydration and reduction gives the unsaturated dibasic acid II, from which by the action of acetic anhydride 6:12-dihydroxychrysene III is formed:

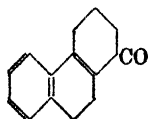


Similarly, methyl cinnamate reduced with aluminium amalgam gives  $\text{CHPh}\cdot\text{CH}_2\cdot\text{CO}_2\text{Me}$  and this on ring closure gives the *cis* and *trans* forms of diketo-hexahydrochrysene from which by reduction and subsequent dehydrogenation with selenium chrysene can be obtained (B., 1931, 2461).

6. *Robinson's method* (J. C. S., 1935, 1288; 1936, 50, 192, 747, 1079), a 5-keto-8-phenyloctoic acid, e.g.  $\text{OMe}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  from the condensation of 4-*m*-methoxybutyryl chloride and ethyl sodio- $\alpha$ -acetylglutarate and elimination of  $\text{CO}_2$ , is made to undergo internal condensation by the action of sodium ethoxide on its ester; the diketone so formed

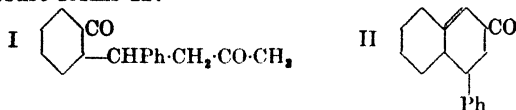


with  $\text{P}_4\text{O}_{10}$  gives keto-hexahydro-phenanthrene



An alternative method is the addition of the sodio-derivative of a saturated ketone to an  $\alpha\beta$ -unsaturated ketone, e.g. sodio-

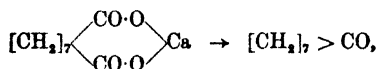
cyclohexanone to styryl methyl ketone yielding I which by ring closure forms II:



By using sodio-cyclohexanone and acetyl-cyclohexene the final product is a reduced phenanthrone, and by using sodio-6-methoxy-1-tetralone and acetyl-cyclohexene the product is a methoxy derivative of a keto-hydrochrysene.

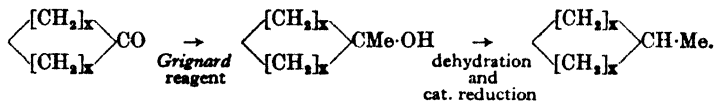
### XXXIII. MANY MEMBERED CARBON RINGS\*

During recent years cyclic ketones containing rings of 9-29 carbon atoms have been prepared in much the same manner as suberone from calcium suberate:

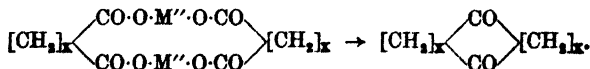


when an 8-membered ring is formed. With the higher homologues of suberic acid the calcium, lead and iron salts are unsuitable, but the thorium and cerium (i.e. quadrivalent metals) salts give the higher membered ketones, although the yields are in many cases small (cf. *Mills*, Thorpe's Dic. Chem. Supp. II, 451).

From these ketones cyclic hydrocarbons may be obtained by the following series of reactions:

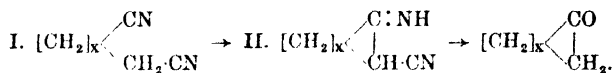


During the formation of the monoketones, diketones are also formed, probably as follows:



\* L. Ruzicka, C. and I., 1935, 2.

A careful examination of the yields shows that the maximum yield of monoketone is obtained with the 6 C ring, viz. 80 per cent, the minimum is reached with 10 C and 11 C rings, viz. 0.1 to 0.2 per cent, but rises again to 8 per cent with 16 C or 17 C rings and then decreases again to an approximately constant value of 2 per cent. For the bigger rings Ziegler (C. and I., 1935, 216) has synthesized the same ketones by a different process, viz. by condensing *n*-aliphatic dinitriles (I) with tertiary *alkali* amines, e.g. lithium or, even better, sodium-methylaniline,  $C_6H_5 \cdot NMeNa$ , and hydrolysing the resulting cyanoketimine (II):



The condensation must be carried out in dilute solution to avoid polymerization and an inflow method is adopted in order to avoid the use of extremely large vessels, i.e. as the nitrile is used up more is run in in order to keep a fixed concentration. With 5, 6 and 7 C rings the yields are good, approximating to 100 per cent, but with 9 C falls below 10 per cent, rises again at 12 C, and reaches a second maximum value of 80 per cent at C 18. Later (A., 1937, 528, 114) rings with 20-27, 29, 30 and 34 C atoms have been prepared by this method. On the whole rings with an even number of carbon atoms give better yields than those with an odd number.

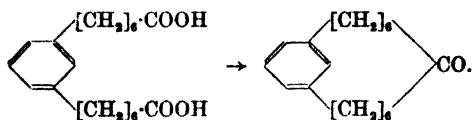
The large membered ketones are stable when heated, and the corresponding hydrocarbons, e.g. C 8, C 15, C 17 and C 30, are stable when heated with hydriodic acid at 250°. The heat of combustion of the different ketones gives a value of approximately 157 Kg. cal. per  $CH_2$ , which corresponds with the value for  $CH_2$  in a paraffin hydrocarbon. These facts indicate that *Baeyer's* view that there is a close relationship between the stability of a ring and the ease with which it is formed does not hold. Determinations of specific gravity and from these of mol. vols. show that the mol. vol. of the  $CH_2$  group decreases continuously from the 4 C (20.4) to the 10 C ring, and then remains practically constant at 16.2-16.3, a value corresponding with the  $CH_2$  value in aliphatic compounds. This points to a similarity in structure between the many membered rings and aliphatic chains, a conclusion confirmed by X-ray investigations (A. Muller), which indicate

that the rings with more than 20 C are composed of parallel double chains, the straight portions of which are identical in structure with the *n*-paraffins. The length of one member of the chain is 1.25 Å in both cases, and the distance between two aliphatic chains (4.45 Å) is also the distance between two parallel portions of a large membered ring. A study of other physical properties, e.g. molecular refraction, parachor and viscosity, show abnormalities in the lower members of the series but a marked similarity between the higher members (C 20 onwards) and aliphatic compounds.

Large rings containing O as part of the ring are known (Stoll and Scherrer, *Helv.*, 1936, 735), e.g.  $\text{O} \begin{array}{c} \text{[CH}_2\text{]}_4 \\ \text{[CH}_2\text{]}_{10} \end{array} \text{CO}$ , which can be reduced to  $\text{O} \begin{array}{c} \text{[CH}_2\text{]}_4 \\ \text{[CH}_2\text{]}_{10} \end{array} \text{CH}_2$ , 1:15-oxidopentadecane; the former has a powerful odour of musk and the latter only a feeble odour.

Ziegler and Holl (*A.*, 1937, 528, 143) state that a ring containing 9 C + 1 O is much more readily obtained than one with 10 C, and the formation of a ring with 11 C + 2 O is less difficult than one with 13 C.

Large rings containing the NH group, viz.  $(\text{CH}_2)_x > \text{NH}$ , with 16-18 members in the ring have been synthesized,\* also a compound,  $[\text{CH}_2]_{13} \begin{array}{c} \text{C} \\ \parallel \\ \text{C} \end{array}$ , with a triple link from the corresponding olefine by addition of  $\text{Br}_2$  and elimination of  $2\text{HBr}$ , and finally large rings condensed with a benzene nucleus in the *meta* and not the usual *ortho*-position:

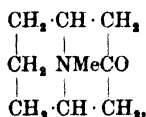


Several compounds containing large membered rings occur naturally. Of these may be mentioned:

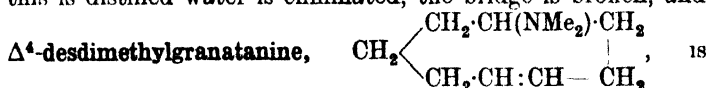
\* For Kinetics see Solomon, *Helv.*, 1936, 743.

## 1. Cyclo-Octane Group

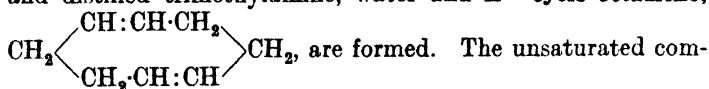
The dicyclic ketone pseudopelletierine present in pomegranate peel,



can be reduced to the corresponding  $\text{CH}_2$  compound, N-methylgranatanine, by means of zinc dust and dilute sulphuric acid, or by electrolytic reduction in dilute acid solution. The methiodide of N-methylgranatanine with moist silver oxide yields the corresponding quaternary hydroxide, and when this is distilled water is eliminated, the bridge is broken, and

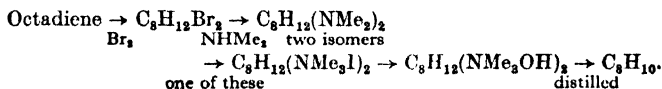


obtained as a colourless oil. When this base is converted into its methiodide, and then into the corresponding hydroxide and distilled trimethylamine, water and  $\Delta^{1:5}$ -cyclo-octadiene,

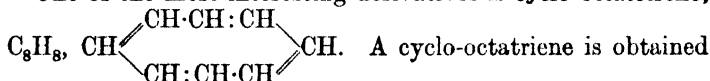


pound is a volatile liquid, boiling at  $39.5^\circ$  under 16 mm. pressure, and polymerizes readily, yielding crystalline hydrocarbons. The  $\Delta^{1:5}$  structure is ascribed to the hydrocarbon on account of the fact that its ozonide, when decomposed by water, yields succinaldehyde,  $\text{CHO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHO}$ , and succinic acid (*Harries*, B., 1908, 671). A more stable isomeride is obtained by heating the dihydrobromide of the  $\Delta^{1:5}$  derivative with quinoline or solid potash. This is a colourless liquid, boiling at  $143^\circ$ – $144^\circ$ , and when reduced by *Sabatier* and *Senderens'* method (Chap. XLIX, A.) yields the saturated compound **cyclo-octane**,  $\text{C}_8\text{H}_{16}$ , a colourless liquid with an odour like camphor, boiling at  $147^\circ$ – $148^\circ$  under 709 mm., and melting at  $14^\circ$ . The presence of an 8-membered ring in the compound is confirmed by its oxidation with nitric acid, when a good yield of suberic acid (Chap. X, A.) is obtained. A **cyclo-octene**,  $\text{C}_8\text{H}_{14}$ , boiling at  $145^\circ$  and readily polymerizing and a **cyclo-octatriene**,  $\text{C}_8\text{H}_{10}$ , are also known.

The latter distils at 36°–40° under 13 mm. pressure, and can be prepared by the following series of reactions:



One of the most interesting derivatives is **cyclo-octatetrene**,



from N-methylgranatenine in exactly the same manner as cyclo-octadiene from N-methylgranatanine, and this, when subjected to the same series of reactions as described above in the conversion of the cyclo-octadiene into a cyclo-octatriene, yields the monocyclic ring compound,  $\text{C}_8\text{H}_8$ , provided the distillation of the quaternary ammonium hydroxide is conducted under a very low pressure at 30°–45°, otherwise compounds are obtained containing one or even two bridges. It is a yellow liquid with a sweet odour, boils at 42.2° under 17 mm. pressure, has melting-point  $-27^\circ$ , and has all the characteristic reactions of olefine compounds. It readily reduces permanganate, absorbs bromine, combines with hydrogen bromide, is readily reduced to cyclo-octane by means of hydrogen and platinum black, and cannot be nitrated or sulphonated. The structure of the molecule is similar to that of benzene, according to *Kekulé* (p. 390), as both consist of a ring of CH groups alternately united by single and double linkings. The complete difference in properties of the two compounds has led *Willstätter* to reject the *Kekulé* formula for benzene and to accept the *Centric* formula.

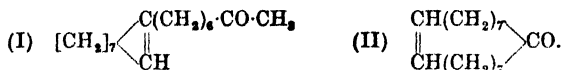
Compare B., 1905, 1975; 1907, 957; 1908, 1480; 1910, 1176; 1911, 3423; 1913, 517.

## 2. Cyclo-Heptadecane Group

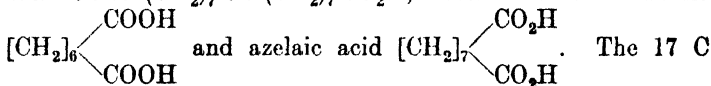
*Civetone*,  $\text{C}_{17}\text{H}_{30}\text{O}$ , is the source of the characteristic odour of the civet, and *muskone*,  $\text{C}_{16}\text{H}_{30}\text{O}$ , is the source of the musk odours. Civetone has all the properties of an unsaturated monocyclic ketone. When oxidized it yields suberic acid and a ketonic acid,  $\text{C}_{17}\text{H}_{30}\text{O}_5$ .

Various structures have been suggested for civetone. The first was a 6-membered ring with a long side chain; this

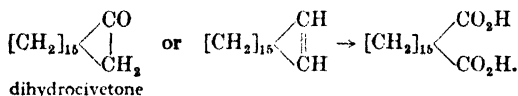
was followed by a 9-membered ring structure I, which was discarded when it was found that dihydrocivetone on oxidation gave the dibasic acid,  $C_{17}H_{32}O_4$ :



The 17 C ring structure II is now generally accepted as it accounts for the formation of the ketonic acid,  $C_{17}H_{30}O_5$ , viz.  $COOH(CH_2)_7 \cdot CO \cdot (CH_2)_7 \cdot CO_2H$ , and also for suberic



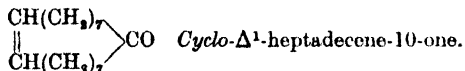
ring structure is also supported by the following relationships. Civetone semicarbazone and sodium ethoxide yield an unsaturated hydrocarbon,  $C_{17}H_{32}$ , with one olefine link, and hence a monocyclic compound. On ozonization this gives a dibasic acid,  $C_{17}H_{32}O_4$ , also formed by the oxidation of dihydrocivetone and identical with the synthetical pentadecanene-1:15-dicarboxylic acid  $CO_2H \cdot (CH_2)_{15} \cdot CO_2H$ .



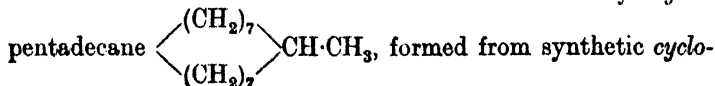
The position of the olefine link in civetone has been proved by the synthesis of the keto-dicarboxylic acid as its methyl ester,  $C_{17}H_{30}O_5$ , from methyl hydrogen azelate,  $CO_2Me \cdot (CH_2)_7 \cdot CO_2H$ , by heating with iron powder.



The structure of the unsaturated ketone is therefore:

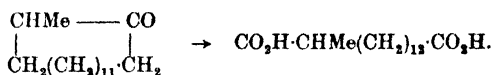


Muskone, on account of its close relationship to civetone, was regarded as methyl *cyclopentadecanone*, and as it is optically active must contain an asymmetric carbon atom. Its structure follows from the fact that the methyl *cyclo-*

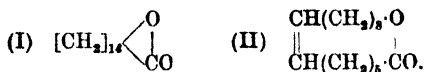




pentadecanone by reaction with magnesium methyl iodide followed by dehydration and subsequent hydrogenation, is identical with the product formed by reducing muskone with amalgamated zinc in hydrochloric acid, i.e. replacement of CO by  $\text{CH}_2$ . The actual position of the methyl with respect to the carbonyl group is proved by the ozonization of benzylidene muskone when 1-methyl-tridecane-1:13-dicarboxylic acid is formed:

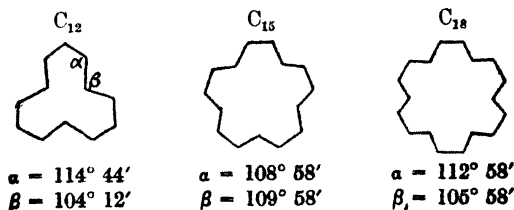


It is interesting to note that the lactones *exaltolide* I from angelica root and *ambrettolide* II from ambretto seed have a characteristic musk odour:



The carbonates  $[\text{CH}_2]_x \begin{array}{c} \diagup \text{O} \\ \diagdown \text{CO} \end{array}$  and anhydrides  $[\text{CH}_2]_x \begin{array}{c} \diagup \text{CO} \\ \diagdown \text{CO} \end{array} \text{O}$  also have musk-like odours when the total number of atoms in the ring is 15–18.

*Drew* (C. and I., 1933, 538) points out that a planar structure is possible for rings containing 12, 15, 18 or 25 C atoms.



### XXXIV. ENLARGEMENT AND DEGRADATION IN RING SYSTEMS

Most of the reactions discussed in the previous chapters have dealt with the conversion of derivatives of a given ring system into others containing the same ring, with the formation of cyclic from open-chain compounds, or with the conversion of ring into aliphatic derivatives.

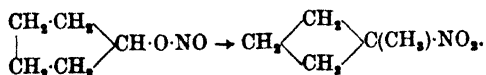
Reactions of considerable theoretical interest, which are occasionally met with, are the conversion of derivatives of one cyclic system into those of another containing one more or one less carbon atom in the ring.

#### A. Degradation

As a rule when a ring compound without side chains undergoes isomerization the product formed is a ring containing a smaller number of carbon atoms, but with side chains.

Thus cycloheptene when reduced gives methylcyclohexane and dimethylcyclopentane.

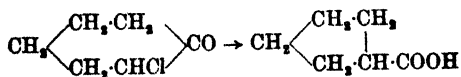
Also cyclopentyl iodide  $\rightarrow$  cyclopentyl nitrite  $\rightarrow$  1-nitro-1-methylcyclobutane:  $\text{AgNO}_3$  Conc. KOH



And 2-iodo-cyclohexan-1-ol with silver nitrite yields 1-aldehydro-cyclopentane (C. R., 1914, 159, 771).

Cycloheptane vapour, when passed repeatedly over platinized charcoal at  $300^\circ$ – $315^\circ$ , yields methylcyclohexane and finally toluenes (J. Gen. Chem. Russ., 1937, 369).

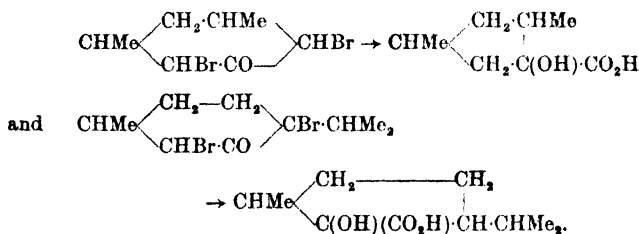
Many  $\alpha$ -chlorinated cyclo-ketones react with alcoholic potash yielding acids derived from a lower ring system:



(J. russ., 1914, 46, 1097).

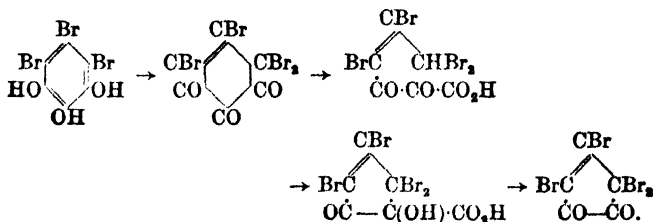
A comparatively simple reaction is the conversion of diphenyl into a mixture of cyclohexane and methylcyclopentane with benzene by the action of  $\text{PCl}_5$  at  $250^\circ$ – $300^\circ$ .

*Wallach* (A., 1918, **414**, 271) has studied the conversion of cyclohexanone into cyclopentanone derivatives. He shows that the dibromide of a cyclohexenone in which the olefine linking is conjugate to the carbonyl group reacts with aqueous alkali yielding a phenol derived from cyclohexane, e.g.  $\Delta^1$ -menthen-3-one yields 2-menthol (Chap. LVII, B2). With a dibromo-derivative in which the two bromine atoms are adjacent to the carbonyl group, but one on each side, the effect of alkali is to form a hydroxy-carboxylic acid derived from cyclopentane, and these can be readily oxidized to cyclopentanone derivatives, e.g.:



*Meerwein* (A., 1914, **405**, 129) shows that when water is eliminated from 1:1-dimethyl-cyclohexan-2-ol by means of oxalic acid the product is a mixture of 75 per cent of the dimethyl- $\Delta^1$ -cyclohexene and 25 per cent of isopropyl- $\Delta^1$ -cyclopentene (cf. C. R., 1928, **186**, 375, 702; A., 1929, **477**, 99).

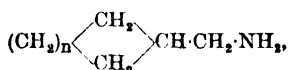
Xanthogallol, a product formed by the action of bromine water on the benzene derivative, tribromopyrogallol,  $\text{C}_6\text{Br}_3(\text{OH})_3$ , is probably a cyclopentene derivative, and its formation can be represented by the following scheme (*Moore and Thomas*, J. A. C. S., 1917, 974):



## B. Enlargement

An example of the enlargement of a carbon-oxygen ring is the conversion of a furanose type of sugar to a pyranose type, i.e. from a 5-membered to a 6-membered ring (Chap. LVI, A).

A fairly general method of increasing the ring by 1 carbon atom is by the action of nitrous acid on a cycloparaffin containing the side chain  $\cdot\text{CH}_2\cdot\text{NH}_2$ , viz.

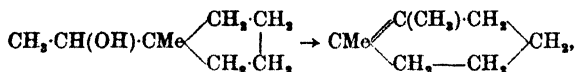


where  $n = 1$  to 4. Thus cyclobutylmethylamine ( $n = 1$ ) gives a mixture of cyclobutylmethanol ( $\text{NH}_2$  replaced by OH) and hydroxy-cyclopentane and the method has been used for preparing certain of the higher cyclic compounds (A., 1907, 353, 325; *Helv.*, 1926, 399; J. C. S., 1928, 1099, 1897).

Ring enlargement from the cyclobutane to the cyclopentane group has been observed by the action of phosphoric anhydride on boiling acetic acid solutions of certain truxinic acids (Chap. L, A1) (B., 1937, 483).

The number of carbon atoms in the ring is frequently increased when a ring compound containing side chains undergoes isomerization; thus 1-methyl-1-iodo-cyclopentane with silver nitrite yields a certain amount of the corresponding 1-nitro-1-methylcyclopentane, together with some nitrocyclohexane, and hydroxymethyl-cyclopentane with oxalic acid yields cyclohexene.

One of the smoothest of such changes is the conversion of 1-methyl-1- $\alpha$ -hydroxyethyl-cyclopentane into 1 : 2-dimethyl- $\Delta^1$ -cyclohexene under the influence of zinc chloride:



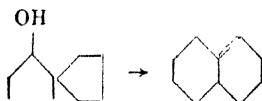
and similarly 1:2:2:3-tetramethyl-1- $\alpha$ -hydroxyethyl-cyclopentane yields 1:2:3:3:4-pentamethyl- $\Delta^1$ -cyclohexene (*Meerwein*, A., 1918, 417, 255).

The pinacone,  $\begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ | \quad | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{C}(\text{OH})\cdot\text{C}(\text{OH}) \begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ | \quad | \\ \text{CH}_2\cdot\text{CH}_2 \end{array}$ , contain-

ing two cyclopentane rings, with dilute sulphuric acid yields

a spiran-pinacolone,  $\begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ | \quad \diagup \\ \text{C} \\ | \quad \diagdown \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ \diagdown \\ \text{CO}\cdot\text{CH}_2 \\ \diagup \end{array} \text{CH}_2$ , in which the one cyclopentane ring has been transformed into a cyclohexane derivative (*Meiser*, B., 1899, 2054).

An interesting ring change is that of 2-cyclopentyl-cyclopentan-1-ol:

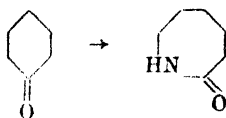


into a mixture of isomeric octahydronaphthalenes by the action of zinc chloride at  $180^\circ$ .

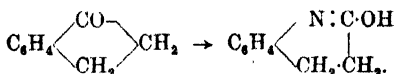
Heterocyclic rings can also undergo enlargement, e.g. pyrrole and diazomethane or  $\text{CH}_2\text{Cl}_2$ , and alkali yield pyridine (cf. Chap. XL and XLIII).

Isatin (Chap. XLI, C.) under the influence of diazomethane has its 5-membered N-ring changed into a 6-membered ring by the addition of  $\text{CH}_2$  (para to NH), and the  $\alpha\beta$  acetal of glycerol in the presence of a trace of acid gives the isomeric  $\alpha\gamma$ -acetal (change from 5 to 6 ring, each with two O).

Another example of ring change with heterocyclic compounds is the action of hydrazoic and sulphuric acids on cyclohexanone and similar compounds (B., 1924, 704; J. C. S., 1937, 456):



Similarly,  $\alpha$ -hydrindone gives dihydro-carbostyryl:



The majority of these ring changes are probably due to an opening of the ring under the influence of the reagents, followed by ring closure.

### XXXV. BEARING OF ELECTRONIC STRUCTURE ON ORGANIC REACTIONS

#### Cationoid and Anionoid Reagents

The two commonest catalytic reagents are protons  $\text{H}^+$ , or the hydrated form  $\text{OH}_3^+$ , and the hydroxyl ion. These are respectively typical *cationoid* and *anionoid* reagents, and *Lapworth* (1920) has attempted to group all other reagents into these two categories. In all reactions in which these reagents take part the anion is an electron donor and the cation becomes an electron acceptor, e.g.  $\text{H}^+ + \text{OH}^- \rightarrow \text{H}_2\text{O}$ . Similarly, anionoid reagents are reducing and cationoid reagents oxidizing agents.  $2\text{Fe}^{++} + 4\text{Cl}^- + \text{Cl}_2 \rightarrow 2\text{Fe}^{+++} + 6\text{Cl}^-$ . The ferrous is oxidized to the ferric state by the chlorine which is itself reduced to the ionic  $\text{Cl}^-$  state.

The following is the definition for the two groups: "If the formation of a covalent bond in the complex A-B takes place by the union of  $\text{A}^+$  with  $\text{B}^-$ , then A is anionoid and B is cationoid". The table (p. 612) gives a list of anionoid and cationoid reagents as drawn up by *Robinson* (1931).\* (*Waters*, p. 181.)

There are great differences in the relative reactivities of anions and cations; for anions the most stable are the least reactive and the reactivity diminishes as the ion more nearly reaches the stable octet valency shell, as illustrated by the increasing reactivity of the anions  $\text{F}^-$ ,  $\text{OH}^-$ ,  $\text{NH}_2^-$ ,  $\text{CH}_3^-$  in the given order.

The activity of a cation depends on its readiness to share an electron pair with an anion. The most stable are  $\text{Na}^+$  and  $\text{K}^+$ , which exist as ions only and cannot form covalent compounds.

#### Organic Cations.

The carbonium cation formed by the basic dissociation of a hydroxylic compound, e.g.  $\text{CH}_3^+$  from  $\text{CH}_3\cdot\text{OH}$  or  $\text{C}_6\text{H}_5^+$  from

\* *Waters, Physical Aspects of Organic Chemistry*, London, 1935. *Robinson, Institute of Chem.*, Lectures, 1932.

ANIONOID OR  
ELECTRON RELEASING

1. Active anions:  $\text{OH}^-$ ,  $\text{CN}^-$ ,  $\text{CH}(\text{CO}_2\text{Et})_2$ , &c.

2. Reducing reagents including all metals and ions which can give up electrons  $\text{Na}$ ,  $\text{Mg}$ ,  $\text{Fe}$ ,  $\text{Fe}^{++}$ ,  $\text{Fe}(\text{CN})_6^{--}$ .

3. Alkyl and aryl residues of organometallic compounds,  $\text{Et}$  in  $\text{Et}\cdot\text{Mg}\cdot\text{Br}$  and  $\text{RC}\equiv\text{C}$  in  $\text{R}\cdot\text{C}\equiv\text{CNa}$ .

4. Donor molecules containing lone pairs of electrons,  $\text{NH}_3$ ,  $\text{C}_5\text{H}_5\text{N}$ ,  $\text{H}_2\text{O}$ ,  $\text{Et}_2\text{O}$ ,  $(\text{CH}_3)_2\text{CO}$ ,  $\text{RSH}$ ,  $\text{R}_2\text{S}$ .

5. Unsaturated carbon in olefines and aromatic hydrocarbons.

## CATIONOID OR ELECTRON ATTRACTING

1. Protons and sources of protons: acids, pseudo-acids and cations from pseudo-bases.

2. Oxidizing agents: halogens, ozone, peroxides and ions which can accept electrons  $\text{Fe}^{++}$ ,  $\text{Fe}(\text{CN})_6^{--}$ ,  $\text{MnO}_4^-$ .

3. Alkyl residues from esters, e.g.  $\text{Me}$  in  $\text{MeI}$  or  $\text{Me}_2\text{SO}_4$  and alkyl groups from quaternary ammonium salts and bases  $\text{Me}$  in  $\text{PhNMe}_3\cdot\text{OH}$ .

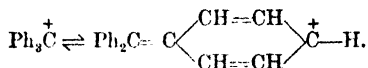
4. Acceptor atoms, ions and molecules which are capable of co-ordination with  $\text{H}_2\text{O}$ ,  $\text{NH}_3$ ,  $\text{Et}$ , e.g.  $\text{ZnCl}_2$ ,  $\text{PtCl}_4$ .

5. Atoms which carry, or easily acquire positive charges, e.g. in semipolar bonds:  $\text{C}$  in  $-\text{CO}$ ,  $-\text{CO}\cdot\text{OEt}$ ,  $\text{CN}$ ;  $\text{S}$  in  $\text{SO}_3$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{NaHSO}_3$ ;  $\text{N}$  in  $-\text{NO}$ ,  $\text{NO}_2$ ,  $\text{HNO}_3$ .

$\text{C}_6\text{H}_5\cdot\text{OH}$  are extremely unstable, as the dissociation of such compounds is usually of the acid type, e.g.  $\text{C}_6\text{H}_5\text{OH} \rightarrow \text{C}_6\text{H}_5\ddot{\text{O}} + \text{H}^+$ .

The formation of a carbonium ion such as  $\text{CH}_3^+$  results in a carbon atom with a sextet shell. Comparatively stable carbonium ions are, however, formed in the case of triphenylmethyl compounds (cf. Chap. LII, B1). The chloride is formed by simple treatment of the hydroxide with  $\text{HCl}$  in benzene solution, and as its solutions are conducting exists largely as  $\text{CPh}_3^+$  and  $\text{Cl}^-$ . The dimeride  $\text{CPh}_3\cdot\text{CPh}_3^+$  also yields conducting solutions, and is present as an equilibrium mixture  $\text{CPh}_3\cdot\text{CPh}_3^+ \rightleftharpoons \text{CPh}_3^+ + \text{CPh}_3$ . The unstable cation  $\text{CPh}_3^+$  probably

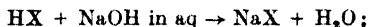
undergoes molecular rearrangement into the more stable and coloured quinonoid form:



Commoner and more stable cations are the oxonium, sulphonium and ammonium ions.

### Organic Anions.

Among the simple organic anions are the aliphyl and aryl groups in their metallic derivatives, e.g. NaEt, Na·CH<sub>2</sub>Ph and NaCPh<sub>3</sub>. These compounds are highly unstable, decompose water, are spontaneously inflammable—except NaCPh<sub>3</sub>—and their solutions in ether, pyridine and liquid ammonia are good conductors pointing to ionization  $\text{EtNa} \rightleftharpoons \text{Et}^- + \text{Na}^+$ . The reaction between  $\text{CHPh}_3$  and  $\text{NaNH}_2$  (sodamide) in liquid ammonia is similar to the neutralization of an acid by a base in water:



where X = CPh<sub>3</sub> in the latter equation.

The compound  $\text{CPh}_3\cdot\text{NMe}_4$  is an organic salt, a strong electrolyte and completely ionized in all solvents, yielding  $\text{CPh}_3^- + \text{NMe}_4^+$ .

The organic cations and anions referred to above are unstable and highly reactive; the ionization is difficult to accomplish, but is facilitated by using solvents of high dielectric constants, especially those of the anionoid type, e.g.  $\text{H}_2\text{O}$ ,  $\text{Et}_2\text{O}$ ,  $\text{Me}_2\text{CO}$ ,  $\text{NH}_3$ (liquid), which can form co-ordination compounds with the reactive cations.

### Organic Acids and Bases.

The common organic acids are carboxylic, sulphonic, phenol and pseudo acids, and all have hydrogen atoms capable of being replaced by metals, and their relative acidities are expressed in terms of proton concentration in the form  $p_{\text{H}}$ :

$$p_{\text{H}} = 1/\log_{10}^+$$

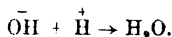


from which it follows that the stronger the acid the lower its  $p_H$  value.

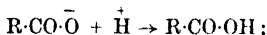
All acids are proton donors and it is customary to group all proton donors as acids, thus the ion  $\text{HSO}_4^-$  is an acid as it gives  $\text{H}^+$  and  $\text{SO}_4^{2-}$ . Under such a definition fall carbonium and oxonium and ammonium ions, as they readily yield protons, e.g.:



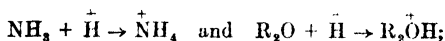
Similarly a base is defined as a proton acceptor. This includes all compounds yielding free  $\text{OH}^-$  ions, as these react readily with protons,



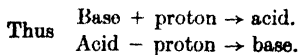
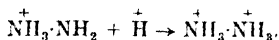
It also includes compounds yielding anions which can discharge protons, e.g.:



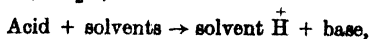
also neutral molecules such as water or ammonia which can combine with protons yielding cations, e.g.:



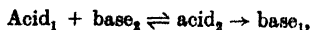
and finally positive charged ions derived from a diacid base (hydrazine), e.g.:



The proton liberated from an acid is unstable as it has no electron shell and hence combines with the solvent—usually water giving the *oxonium ion*  $\text{H}_3\text{O}^+$ —but also with other solvents, e.g.  $\text{EtOH}$ ,  $\text{Et}_2\text{O}$ , &c. Hence



or neutralization consists in the transfer of a proton from combination with one base, e.g.  $\text{OH}^-$  to another base, e.g.  $\text{H}_2\text{O}$ , or generally:

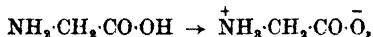


This reaction is reversible and roughly 50 per cent reacts giving acetate and anilinium ions.

As already pointed out (p. 185) the relative strengths of acids are represented by their dissociation constants. These constants are usually those determined by *Ostwald* or by his method, and are termed by *Watson* "Classical dissociation constants". More modern determinations by *Dippy* and others (J. C. S., 1934-1939) by the conductometric method, making corrections for frictional resistance of the medium, inter ionic attraction and Brownian movement of the ions, are termed "thermodynamic dissociation constants".

In the case of fatty acids attention has been drawn to the fact that certain substituents tend to increase the strength of an acid and others to diminish the strength as compared with that of the unsubstituted acid. The former are termed **acylous** and the latter **basyulous** by Lapworth, and these expressions are preferable to the older terms negative and positive. The most strongly acylous group is the nitro, others are halogens,  $-\text{CN}$ ,  $-\text{CH}(\text{CO}_2\text{Et})_2$ , which can form free anions and phenyl. Feebly basyulous is  $-\text{CH}_3$  as shown by a comparison of propionic and acetic acids, more acylous is  $\cdot\text{CMe}_2$  and strongly basyulous is  $\cdot\text{CO}\cdot\bar{\text{O}}$  as shown by a comparison of  $\text{CO}_2\text{H}\cdot\text{R}\cdot\text{CO}_2\text{H}$  and  $\text{CO}_2\text{H}\cdot\text{R}\cdot\text{CO}\cdot\bar{\text{O}}$ , the second dissociation constant  $K_2$  of a dibasic acid being always much smaller than the 1st constant  $K_1$  (cf. p. 264).

The amino-group often forms an inner salt with the carboxylic group (cf. Betaines, p. 245), e.g.:



but is of the acylous type as  $\text{NHPh}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  is a stronger acid than  $\text{CH}_2\text{Ph}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  (ratio 3.9:2.3), and similarly  $\text{NPh}(\text{CO}_2\text{H})_2$  is stronger than  $\text{CHPh}(\text{CO}_2\text{H})_2$ .

Unsaturated acids as a rule are stronger acids than their saturated analogues, e.g. propionic acid 1.8 and acrylic 5.6, but the value of  $K$  varies greatly with the position of the double bond. The  $\beta\gamma$  acid is always the strongest and in the hexenoic acids the strength rises and falls from the  $\alpha\beta$  to the  $\delta\epsilon$  acid, e.g. 1.89, 2.64, 1.74, 1.91. This and similar phenomena may be due to the zigzag structure of the carbon chain.

The same acylous group increases the strength of phenols

as illustrated by the following values for  $K \times 10^9$ : phenol 0.11, *o*-nitro 68, *m*-nitro 3.9, *p*-nitro 70, picric acid  $1.6 \times 10^{-1}$ ; whereas they reduce the dissociation constant of aniline from  $5.7 \times 10^{-10}$  for aniline to  $1.0 \times 10^{-14}$  for *o*-nitroaniline.

## Inductive and Tautomeric Effects

Two electron displacement factors affecting the activity of a molecule are the inductive and tautomeric effects.

### 1. Inductive Effect.

In a symmetrical compound, e.g.  $\text{CH}_3\cdot\text{CH}_3$  or  $\text{NH}_2\cdot\text{NH}_2$ , the electrons of the covalent links are equally shared so that no permanent polarization can be detected. When, however, a chlorine atom enters the methane molecule it does not follow that in the covalent bond between C and Cl the electrons are shared equally. One atom has a slight extra + and the other a corresponding - charge, there is a small static displacement of the electron pair, i.e. polarization within the stable valency shell, and the compound exhibits a dipole moment (Chap. LXXI, G.).

In the case of  $\text{CH}_3\text{Cl}$  the chlorine is electron attracting, so that the condition may be represented as  $\overset{\delta+}{\text{H}_3\text{C}}-\overset{\delta-}{\text{Cl}}$ ,  $\overset{\delta+}{\text{H}_3\text{C}}-\overset{\delta-}{\text{Cl}}$ , or  $\text{H}_3\text{C} \rightarrow \text{Cl}$ , and the limiting case occurs where the Cl breaks away as the ion  $\bar{\text{Cl}}$  leaving the  $\overset{+}{\text{CH}_3}$  cation.

In the compound  $\text{H}_3\text{C}-\text{Mg}-\text{Br}$  the dipole is in the opposite direction, indicating that the electron concentration is greater on the C and not on the Mg,  $\text{CH}_3 \leftarrow \text{MgBr}$ . Groups like  $\text{NO}_2$ , Cl, CN are termed electron attractive and their effect is denoted by +I; whereas the MgBr group and also the  $\text{CH}_3$  group in  $\text{CH}_3\text{Cl}$  are electron releasing and denoted by -I.

The following list taken from *Gilman* gives the relative inductive effects of various atoms and ions:

#### (1) *Electron Release* - I.

(a) Anions.  $-\bar{\text{NR}} > -\bar{\text{O}} > -\bar{\text{S}} > -\bar{\text{Se}}$ .

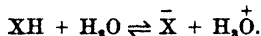
(b) Radicals.  $-\text{Li} > -\text{MgX} > -\text{ZnX} > -\text{CaX} > -\text{HgX}$   
 $-\text{AlR}_3 > -\text{SiR}_3 > -\text{SnR}_3 > -\text{PbR}_3$   
 $-\text{CMe}_3 > -\text{CHMe}_3 > -\text{CH}_2\text{Me} > -\text{CH}_3$ .

(2) *Electron Attraction + I.*

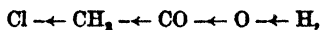
- (a) Cations.  $-\overset{+}{\text{OR}}_2 > -\overset{+}{\text{NR}}_2 > -\overset{+}{\text{PR}}_2 > -\overset{+}{\text{AsR}}_2$   
 $-\overset{+}{\text{OR}}_2 > -\overset{+}{\text{SR}}_2 > -\overset{+}{\text{SeR}}_2$   
 $-\overset{+}{\text{NR}}_2 > -\text{NR}_2$  and  $-\overset{+}{\text{OR}}_2 > -\text{OR}.$
- (b) Radicals.  $-\text{NH}_2 > -\text{NO}_2 > -\text{AsO}_2\text{H}_2$   
 $-\text{SO}_2\text{R} > -\text{SOR}$  and  $-\text{SO}_2\text{R} > -\text{SO}_2-$   
 $-\text{F} > -\text{OR} > \text{NR}_2$   
 $-\text{F} > -\text{Cl} > -\text{Br} > -\text{I}$   
 $-\text{C} \equiv \text{CR} > -\text{CR} = \text{CR}'-$

Great care is required in dealing with the signs + and - in connexion with I. *Ingold* termed electron release effects +I and electron attraction -I, but *Robinson* (*loc. cit.*, p. 34) points out that the sign should logically denote the charge induced, thus  $-\text{MgX}$  produces an increase in electron density on the group to which it is attached, and a decreased electron density on itself, and hence should be termed -I and not +I. *Robinson*, in this country, and *Gilman*, in America, adopt this system, but *Ingold's* classification is still largely used in English chemical literature.

The results of inductive effects are seen in the ionization constants of acids, which are a measure of the tendency of the molecule to discard protons and form anions or a competition between the anion and a water molecule for the proton.



By introducing a chlorine atom into the acetic acid molecule, the chlorine tends to attract electrons from the adjoining carbon atom and this produces an induced effect upon the C atom of the  $\cdot\text{CO}_2\text{H}$  group and then on the O of the  $\cdot\text{OH}$ , and finally on the H,



thus facilitating the liberation of  $\overset{+}{\text{H}}$ . The same argument holds good for all acylous groups in the  $\alpha$ -position in a fatty acid, and their relative effects are indicated in the table above, where the positionally charged cations will have the greatest effect. For list of values of  $K \times 10^5$  for substituted fatty acid cf. p. 192, and for aromatic acids p. 514.

The inductive effect in a saturated carbon compound

diminishes rapidly, and become negligible beyond 2 or 3 atoms, hence an electron-attracting group in the  $\gamma$  or  $\delta$  position in a fatty acid has but little effect on the dissociation constant, as shown by the following values for  $K \times 10^5$ : chloroacetic 155,  $\beta$ -chloropropionic 8.5,  $\gamma$ -chlorobutyric 3, and  $\delta$ -chlorovaleric 2.

The groups which tend to increase the dissociation constant of an acid also tend to increase the strength of a phenol as an acid, as illustrated by the nitrophenols, but in these cases the electromeric factor is also involved.

A careful examination of the dissociation constants of substituted acetic acids,  $XCH_2COOH$ , and of the dipole moments of substituted hydrocarbons,  $CH_3X$ , shows that there is a simple quantitative relationship between the two sets of figures and a smooth curve is obtained when the logs of  $K$  are plotted against the values for  $\mu$  of the corresponding substituted hydrocarbons. This curve is denoted by  $\log K = \log K_0 - C(\mu + a\mu^2)$ , where  $K$  = dissociation constant of the substituted acid,  $K_0$  that of the unsubstituted acid,  $\mu$  is the dipole moment, and  $C$  and  $a$  are constants. This simple relationship does not hold good with substituted benzoic acids.

## 2. Tautomeric Effect T.

This is largely a dynamic polarizability associated with multiple covalent bonds and with atoms with unshared electron pairs. In reality two factors are involved—the more important dynamic polarizability often termed electromeric E and a permanent polarization factor—mesomeric M. So that  $T = E + M$ . The dynamic polarization is largely affected by reagents and solvents. In the case of an unsaturated compound  $-A=B-$ , when A and B are dissimilar the 4 electrons involved in the double link will not be equally shared even in the resting states, and on activation by reagents there will be a further tendency for electron displacement, and if this is complete the state  $-\overset{+}{A}-\overset{-}{B}-$  or  $-\overset{-}{A}-\overset{+}{B}-$  is reached, the displacement may, however, not be complete and the symbols

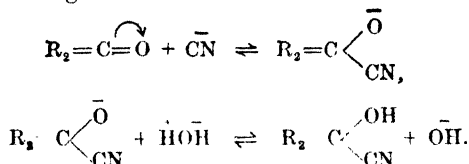
$\curvearrowright A=B$  and  $\curvearrowleft A=B$  are commonly used to indicate the

tendency for the electron pair constituting one of the double bonds to migrate to one or other of the two atoms joined by

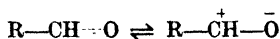
the double bond. The general rule is that the atom with the higher effective nuclear charge, i.e. O in  $C=O$ , and N in  $C\equiv N$ , retains the electron pair, so that in the carbonyl compound

$R-CH=O$  we have  $R-CH\overset{+}{C}=O$ , or if complete  $R-\overset{+}{CH}-\bar{O}$ .

or as it may be put,  $R-CH-\overset{+}{C}O$ . It is clear that in such a state the positive C atom has a valency shell of 6 instead of the stable octet, and hence in a reaction of a carbonyl compound the point of attack is the  $+C$  atom as demonstrated by *Lapworth* in the cyanhydrin reaction of ketones, which takes place in the stages:

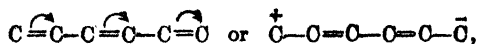


If no suitable anionoid reagent is present to react with the  $+C$  then there is a tendency for the equilibrium



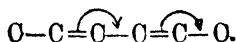
to favour the change from right to left.

The reaction of olefines with halogens, nitric acid, ozone and acids giving protons, i.e. powerful cationoid reagents and their non-reaction with alkalis, amines and *Grignard* reagents, indicate that olefines and also benzene are anionoid in character, i.e. in the reactive stage  $>\overset{+}{C}-\bar{C}<$  the first addition occurs at the  $\bar{C}$  (cf. Addition of Br to olefines in Chap. LI, B.). In a conjugated system containing alternate single and double bonds the polarization may proceed along the complete chain,



and hence the electromeric or tautomeric effect, i.e. electronic displacements can be affected by a given group for appreciable distances along such a conjugate system. At the same time it is to be noted that a single becomes a double link and vice

versa, and this is denoted by a curved arrow passing over the C atom (*Robinson*).



For further details cf. Chap. LI, Unsaturation.

### + or -T effects of different groups

+T

Amino and substituted amino-groups

+I and +T

Halogens, alkyloxy (only weak +I)

+I and -T

Carbonyl, carbethoxy, cyano.

## Reactions of Organic Halides

Among the commoner reactions are:

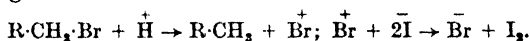
- (1) Replacement of one halogen by another.
- (2) Replacement of halogen by hydrogen.
- (3) Hydrolysis of alkyl halides.
- (4) Hydrolysis of acyl halides.

1. It is well known that in many cases a chloro-derivative can be converted into the corresponding iodo-derivative by boiling with an aqueous or aqueous-alcoholic solution of potassium iodide. This is a simple exchange of electrons from  $\bar{\text{I}}$  to  $\text{Cl}$ , and is attributable to the diminution in the electric discharge potential of the halogens with increasing atomic weight or atomic number; in other words, to the intervening shells of electrons between the valency electrons and the central nucleus. Similarly, organic iodides are more reactive than the corresponding chlorides, e.g. in the formation of *Grignard* reagents, in reactions with ammonia, &c., due to the fact that it requires greater energy to release the electrons from  $\text{Cl}$  than from  $\bar{\text{I}}$ . The effect of substituents on the reaction velocity of aliphyl chlorides,  $\text{R}(\text{CH}_2)_n\text{Cl}$  with  $\text{KI}$  has been studied by *Conant* and others (*J. A. C. S.*, 1924-29) by simply titrating the excess of  $\bar{\text{I}}$  in the presence of iodate and hydro-

chloric acid. In all cases the effect of R diminishes rapidly as the number of  $\text{CH}_2$  groups increases, exactly as with the dissociation constants of acids, and after four  $\text{CH}_2$  groups is negligible. The reaction of the compound is greater when R is an acylous group, as indicated by the diminishing order:  $\text{Ph}\cdot\text{CO}\cdot$ ,  $\text{MeCO}\cdot$ ,  $\cdot\text{CN}$ ,  $\cdot\text{CO}_2\text{Et}$ ,  $\text{OMe}$ ,  $\text{Ph}$ ,  $\text{CH}_2\cdot\text{CH}\cdot$ ,  $\text{C}_3\text{H}_7\cdot$ .

## 2. Replacement of halogen by hydrogen. Inverse Substitution.

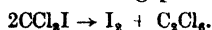
This replacement is usually effected by reduction, and the reaction of alkyl halides with hydriodic acid has been studied in detail. The reaction probably depends on the liberation of halogen cations, e.g.  $\text{Br}^+$ , which react with the iodide anions liberating free iodine:



Acylous groups such as  $\text{NO}_2$  and halogens increase the reactivity.

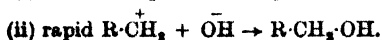
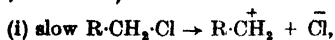
With polyhalide derivatives, e.g.  $\text{CBr}_4$ ,  $\text{CHBr}_3$ ,  $\text{CHI}_3$ , the replacement takes place in the presence of alkalis when an atom of Br or I is liberated as a positive ion which reacts with the  $\text{OH}^-$  yielding  $\text{Br}\cdot\text{OH}$  or  $\text{I}\cdot\text{OH}$ .

Iodine is liberated so readily that tetrahalogenated compounds readily lose iodine forming perhalogenated ethanes:



Inverse substitution occurs extremely readily with halogen derivatives of compounds with acid properties, e.g. containing a reactive  $\text{CH}_2$  or  $\text{NH}$  or  $\text{NH}_2$  group. Examples are ethyl bromomalonate,  $\text{CHBr}(\text{CO}_2\text{Et})_2$ , and dichloramine T,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\cdot\text{NCl}_2$ . The halogen-free compounds liberate protons and the halogen derivatives yield positively charged halogen atoms, as proved by the fact that the acidified compound liberates iodine from potassium iodide solutions (cf. above).

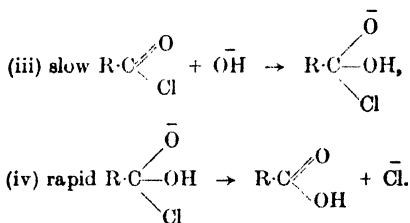
3. The hydrolysis of alkyl chlorides in aqueous-alcohol or acetone is the opposite of 1 and 2 as acylous substituents such as  $\text{NO}_2$  and  $\text{CO}_2\text{H}$  tend to diminish the rate, whereas basylous groups, e.g.  $\text{OMe}$  and  $\text{Me}$ , increase the rate. With tertiary alkyl halides the reaction proceeds in the stages (*Hughes and Ingold*, J. C. S., 1935-38):





When acylous groups are present, as in benzyl chlorides or bromides, the *meta* compound has the highest velocity, whereas with basylous groups the *meta* compound reacts much more slowly than the isomeric *ortho* and *para* compounds.

4. The hydrolysis of acyl halides is different from (3) and resembles (1) and (2) in the fact that the velocity is increased by the introduction of acylous groups and it is probable that the reaction occurs in the stages:



Comparing equation (i) above with (iii), it is clear that they have opposite polar characters, as in (i) the organic radical donates a pair of electrons to the halogen atom and in (iii) it accepts a pair from the OH. Hence polar substituents will affect the two reactions in opposite ways.

5. The elimination of hydrogen bromide from N-brominated substituted benzamides,



by the action of a large excess of NaOH at 30° in the case of *m*- and *p*-substituted compounds is polar and the relative rates are inversely related to the dissociation constants of the corresponding benzoic acids, indicating that the reaction depends on the readiness of release of a negative bromine ion (J. A. C. S., 1937, 121).

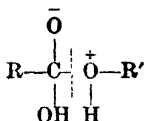
## Hydrolysis

This is the name given to reactions in which water takes part and produces the breaking of a covalent bond in the compound by the addition of H and OH; numerous examples have already been given in the case of alkyl halides, acyl chlorides, esters, acid amides, nitriles, &c. All the reactions

with organic compounds are relatively slow and have a distinct energy activation, and in these two respects differ completely from the hydrolysis of salts. The process is ionic and involves the  $\overset{+}{\text{H}}$  and  $\text{OH}^-$  of water or added hydrions and hydroxyl ions provided by the catalyst, i.e. free acid or alkali. The hydrolysis of an ester can take place with water alone and becomes rapid when acylous groups are present, e.g. ethyl chloroacetate, ethyl tartrate, and, of course, varies with the solubility of the ester in water. As comparatively few esters are readily soluble in water, aqueous alcoholic solutions of mineral acids or alcoholic potash are often employed.

In acid hydrolysis, e.g.  $\text{HCl}$ , the  $\text{Cl}^-$  ion remains intact throughout the reaction, and with alkaline hydrolysis, e.g.  $\text{KOH}$ , the  $\text{K}^+$  ion remains intact, hence the  $\overset{+}{\text{H}}$  is involved in acid hydrolysis and the  $\text{OH}^-$  in alkaline hydrolysis. With esters of strong acids and water the acid formed liberates much hydrion and hence the reaction is autocatalytic.

An ester has two points of attack: (1) The cationoid carbonyl group which can attract an anion, e.g.  $\text{OH}^-$ , and (2) the  $\text{OR}$  group which can attract a cation ( $\overset{+}{\text{H}}$ ) to form an onium salt. In reality both groups are utilized in the process of hydrolysis, and both  $\overset{+}{\text{H}}$  and  $\text{OH}^-$  ions are added to the ester molecule, forming a dipolar molecule, and in both acid and alkaline hydrolysis of the ester  $\text{R}\cdot\text{CO}\cdot\text{OR}'$ , this intermediate product is the same:

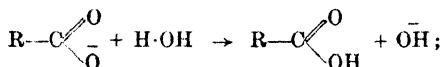


and by a flow of electrons from atom to atom in this dipolar molecule a disruption at the central  $\text{C}-\text{O}$  bond takes place yielding a molecule of acid and of alcohol. The alkyl group of the ester is eliminated as an alcohol molecule and not even primarily as a free cation. This is clear from the fact that an ester containing an alkyl group which can, in the form of a cation, undergo isomeric change is eliminated unchanged in the alcohol formed.

A direct proof that fission occurs at the position indicated by the dotted line is afforded by the fact that both in hydrolysis by mineral acid and also by alkali, using as solvent water containing heavy oxygen (Chap. LIV), the heavy oxygen is never found in the alcohol formed but in the organic acid.

The reactions involved in hydrolysis are: (1) The addition of  $\text{H}^+$  (in acid hydrolysis) or  $\text{OH}^-$  (in alkaline) to the ester. (2) The collision of the complex ion with water molecules and the formation of the dipolar molecule. (3) Instantaneous rupture of the C—O bond by flow of electrons (*Moellwyn-Hughes*, *Phil. Mag.*, 1932, **14**, 112).

The acid or alkali used as catalyst cannot give substantial concentrations of both  $\text{H}^+$  and  $\text{OH}^-$ , and hence in acid solutions the  $\text{OH}^-$  and in alkaline solutions the  $\text{H}^+$  must be derived from molecules of water. Any proton donor can supply the cation, but the supply of  $\text{OH}^-$  can only come from a hydroxy compound. Acid anions, e.g.  $\text{CH}_3\text{CO}_2^-$ , are not direct sources of  $\text{OH}^-$ , but they can react with water to supply  $\text{OH}^-$ , but the acetate ion has only about 1/30,000 the efficiency of an  $\text{OH}^-$ .



The rate of hydrolysis of a simple ester or the inversion of sugar by different dilute acids was utilized by *Arrhenius* and *Ostwald* for determining the degree of dissociation of the acids, but the reaction is much more complex, as with a strong mineral acid the hydrolysis of cane sugar is greatest in concentrated solutions where the  $\text{H}^+$  concentration is small. *Dawson* (*J. C. S.*, 1926–36) claims that the velocity coefficient is a sum of the partial reaction velocities of hydron, hydroxyl ion, undissociated molecules of acid and anion.

$$\begin{aligned} v &= v_{\text{H}^+} + v_{\text{OH}^-} + v_{\text{M}} + v_{\text{A}^-} \\ &= k_{\text{H}^+} [\text{H}^+] + k_{\text{OH}^-} [\text{OH}^-] + k_{\text{M}} [\text{HA}] + k_{\text{A}^-} [\text{A}^-]. \end{aligned}$$

where [ ] represents the concentration of the different ions or molecules.

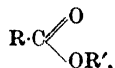
By working with a weak acid of concentration  $c$ ,  $[\bar{A}] = [\bar{H}]$ ,  $[\bar{OH}] = \text{nil}$ ,  $[HA] = c - [\bar{H}]$ ,  $k_A = [\bar{H}] \times [\bar{A}]/[HA]$ . Then

$$v = (k_H^+ - k_M^+)[\bar{H}] + k_A^- \frac{K_A c}{[\bar{H}]} + k_M c - k_A^- K_A,$$

where  $K_A$  is the dissociation constant of the acid.

When the velocity of a reaction, which is catalysed by both  $\bar{H}$  and  $\bar{OH}$  ions, is plotted against hydrogen ion concentrations, a symmetrical curve is obtained with a minimum velocity corresponding with a given  $\bar{H}$  concentration, viz.  $\bar{H}_1$ , and this is proportional to the square root of the concentration of the catalysing acid.

Polar groups play an important part in the velocity of ester hydrolysis and *Ingold* (J. C. S., 1930-36) claims that in an ester



where steric effects are eliminated the ratio  $C = k_{\bar{OH}}^-/k_H^+$  is a function of the polarities of the groups R and R'. This has been tested in the two groups of esters,  $\text{X} \cdot \text{CO} \cdot \text{O} \cdot \text{CH}_2\text{Y}$  and  $\text{XCH}_2 \cdot \text{CO} \cdot \text{O} \cdot \text{CH}_2 \cdot \text{CH}_2\text{Y}$ , and the results indicate that electron-attracting (acylous) groups, e.g. Cl, Ac,  $\text{NH}_3^+$ , favour hydrolysis by  $\bar{OH}$ , whereas electron-donating (basyous) group, e.g.  $\text{CH}_3$ , favour hydrolysis by  $\bar{H}$ , when the group is present in either the alkyl or acyl radical.

For esters of glyceric acid,  $\text{OH} \cdot \text{CH}_2 \cdot \text{CH}(\text{OH}) \cdot \text{COOR}$ , with the value  $p_H^+ = 4.3$  corresponding with the minimum velocity coefficient, the ratio  $k_{\bar{OH}}^-/k_H^+$  is of the order  $11 \times 10^{-3}$  and varies from  $27.5 \times 10^{-3}$  for Me to  $5.8 \times 10^{-3}$  for isopropyl, indicating that alkyl groups favour hydrolysis by  $\bar{H}$ , but that the effect is neutralized by the interposition of 3 or more  $\text{CH}_2$  groups.

With esters of symmetrical dibasic acids the ratio of the velocity of acid hydrolysis of the first ester group  $k_1$  to that for the second ester group  $k_2$  is 2, but this does not hold good for alkali hydrolysis and can reach a value of  $10^4$  in the case of methyl and ethyl oxalates, but falls in the oxalic series

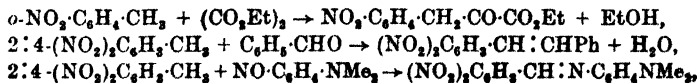
until it reaches a roughly constant value of 3 at methyl suberate. This is due to the fact that the product of the first hydrolysis is an anion,  $\text{RO}\cdot\text{CO}\cdot(\text{CH}_2)_n\cdot\text{CO}\cdot\bar{\text{O}}$ , which will tend to repel  $\text{OH}$  from the vicinity of the second ester group and thus depress the value  $k_2$ . From the results of the ratio  $k_1/k_2$  it has been found possible to calculate the intramolecular distance between the two  $\text{CO}_2\text{H}$  groups.

### XXXVI. STERIC EFFECTS

The effect which a substituent can produce on the course of a reaction may be due to at least two different causes. Its own electronic properties may modify the general electric conditions of the molecule so as to produce a marked effect upon the chemical reactivity of the substance into which it has been introduced. The effect is polar in character and will differ according to the acylous or basylous nature of the substituent. Numerous examples have been already mentioned (cf. Chap. XXXV).

One of the most interesting of these is the increased reactivity of a chlorobenzene when *o*- and *p*-nitro-groups are present. The increased activity is so marked in *s*-trinitrochlorobenzene, picryl chloride, that the compound behaves more like an acyl chloride. The same holds good of the corresponding amino- and ethoxy-compounds; thus picryl amide has more the properties of an acid amide than an alkylamine, and *s*-trinitroethoxybenzene the properties of an ester rather than of an ether. As already indicated these properties are largely due to the polar character of the nitro-group. This reactivity of halogen when *o* and *p* to nitro-groups is of great value in synthetical chemistry, e.g. 2 : 4-dinitrochlorobenzene reacts so readily that the chlorine can be replaced by  $\text{OEt}$ ,  $\text{OPh}$ ,  $\text{NH}\cdot\text{NH}_2$ ,  $\cdot\text{CNS}$ ,  $\cdot\text{NHPh}$ , or  $\cdot\text{CH}(\text{CO}_2\text{Et})_2$ ,  $\text{CH}(\text{CN})\cdot\text{CO}_2\text{Et}$ .

Nitro-groups ortho and para to a methyl group render the latter reactive and capable of condensing with aldehydes, esters, &c.:

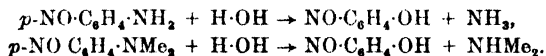


In the last reaction the product, an azomethine, can be readily hydrolysed to 2 : 4-dinitrobenzaldehyde.

Nitro-groups can also activate the hydrogen of a benzene ring, thus *m*-dinitrobenzene and hydroxylamine in the presence of sodium ethoxide yield 2 : 4-dinitroaniline and 2 : 4-dinitrophenylene-diamine by the replacement of the H atoms adjacent to NO<sub>2</sub> groups by NH<sub>2</sub> groups. Similarly, *m*-dinitrobenzene and potassium cyanide in methyl alcoholic solution yield 2 : 6-dinitrobenzonitrile.

Other electron-attracting groups (acylous), e.g. CO<sub>2</sub>H, CHO, ·SO<sub>3</sub>H, ·CN, ·CO·R produce effects similar to the nitro-group, but not to the same extent (B., 1916, 2222), and it is to be noted that all these acylous groups have a *meta* orientating effect in benzene substitution.

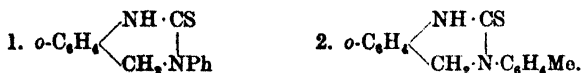
In the true aromatic amines it is not possible to replace ·NH<sub>2</sub> or even ·NMe<sub>2</sub> by OH by means of ordinary hydrolysing agents such as aqueous alkali, but the introduction of a *para*-nitroso group gives a product which is readily hydrolysed:



This reactivity of NH<sub>2</sub> groups is met with in the naphthylamines with acids or alkalis; more particularly with sodium bisulphite they yield naphthols, which in their turn are readily transformed back into the amines by ammonium sulphide. The naphthols and also  $\alpha$ - and  $\beta$ -anthranol and phenanthranol react with alcohols and an acid catalyst, yielding ethers in exactly the same manner as acids yield esters, and these ethers are hydrolysed by alkalis to the alcohol and hydroxy compound.

The reactivity of Cl in triphenylchloromethane, CPh<sub>3</sub>Cl (Chap. LII, B1), is very marked, the compounds react with hydroxy compounds, e.g. alcohols, hydroxy esters and sugars in pyridine solution, yielding ethers CPh<sub>3</sub>·OR (B., 1923, 766; 1925, 872).

The marked effect produced by an *ortho*-methyl substituent is met with in the reduction of the two compounds:



The former retains its ring structure with CS replaced by

$\text{CH}_2$ , the latter loses the  $\text{CS}$  group as  $\text{CH}_3\text{SH}$  and yields the *o*-compound  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{Me}$ .

Substituents in an acid, either aliphatic or aromatic, render the elimination of carbonic anhydride more easy. Acetic acid at  $390^\circ$  is unchanged, whereas malonic acid,  $\text{CH}_2(\text{CO}_2\text{H})_2$ , readily eliminates carbon dioxide at much lower temperatures; nitroacetic acid and hot water yield nitro-methane and carbonic anhydride, and this acid is an intermediate product in the formation of nitro-methane from chloroacetic acid and sodium nitrate.

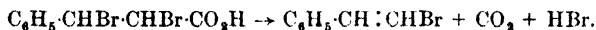
The introduction of the nitro-groups into benzoic acid gives *s*-trinitrobenzoic acid, which is quantitatively converted into *s*-trinitrobenzene when boiled with water, and this serves as the most convenient method for preparing the nitrated hydrocarbon.

*o*- and *p*-hydroxy groups also facilitate removal of  $\text{CO}_2$ , e.g. resorcinol is formed when 2 : 4-dihydroxybenzoic acid is boiled with water.

There is considerable difference in the readiness with which the acids (1)  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ ; (2)  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ ;

(3)  $\begin{array}{c} \text{C}_6\text{H}_4 \\ | \\ \text{CH} \\ | \\ \text{C}_6\text{H}_4 \end{array} \text{CO}_2\text{H}$ ; (4)  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$  lose carbonic anhydride: (1) at  $350^\circ$ – $375^\circ$  gives toluene; (2) is only slightly changed at  $370^\circ$ ; (3) readily yields fluorene at  $220^\circ$ – $230^\circ$ , and (4) yields styrene when distilled very slowly.

When an aqueous solution of cinnamic acid dibromide is warmed with aqueous sodium carbonate both  $\text{HBr}$  and  $\text{CO}_2$  are eliminated and a bromostyrene is formed:



A convenient method for eliminating carbonic anhydride is to heat the acid with pyridine, quinoline, aniline, or dimethylaniline.

In practically all the above reactions the polarity of the substituent is an important factor; there are, however, reactions which can be retarded by substituents of both acylous and basylous types, and it is probable that in such reactions the introduction of a group comparatively large with regard to the hydrogen displaced may so occupy the space around the reactive group that the reagent cannot easily come into contact with it.

This effect of space-filling is often termed **steric hindrance**, but it should be borne in mind that polar factors also play their part in such reactions.

## Steric Hindrance

This phenomenon was first studied in experiments on **catalytic** esterification. *V. Meyer* and *Sudborough* (B., 1894, 510, 1580, 3146) observed that, although benzoic acid and most of its substituted derivatives are completely esterified when left overnight dissolved in, or in contact with, methyl alcohol saturated with hydrogen chloride or when boiled with a 3 per cent solution of hydrogen chloride in methyl alcohol; acids in which both *ortho*-positions are substituted yield no ester under these conditions.

The inhibition is characteristic of all substituents whether of acylous or basylous character, e.g. OMe, Me, Cl, Br, I, NO<sub>2</sub>, CO<sub>2</sub>H, CN, &c. The view put forward was that these groups occupy space around the carboxylic group and prevent the

formation of an additive compound  $\text{R}-\text{C} \begin{array}{l} \nearrow \text{OMe} \\ \text{---} \text{OH} \\ \searrow \text{OH} \end{array}$ , which, on loss of water, gives the ester (*Wegscheider*).

In harmony with this view is the fact that if the CO<sub>2</sub>H group is removed from the ring by the interposition of ·CH<sub>2</sub>·CH<sub>2</sub>, then an ester can be obtained in the normal manner even when *o*-substituents are present, thus *s*-tribromophenylpropionic acid, C<sub>6</sub>H<sub>2</sub>Br<sub>3</sub>·CH<sub>2</sub>·CH<sub>2</sub>·CO<sub>2</sub>H, is readily esterified. Later experiments by *Kellas* (Zeit. phys. Chem., 1897, **24**, 221), by determining the velocity coefficients of various substituted benzoic acids, proved that one *ortho*-substituent has a retarding effect, and subsequent investigations have proved that retardation of esterification by the introduction of substituents in close proximity to the carboxylic group is very general. In the normal fatty acid series formic acid is most readily esterified and the velocity coefficient then falls and becomes practically constant at butyric and from C<sub>4</sub> to C<sub>18</sub> the value is practically the same. The introduction of a substituent, e.g. methyl or halogen, has the greatest retarding effect in the  $\alpha$ -position, a less effect in the  $\beta$ -position, and has practically no effect when in the  $\delta$ -position, or still further removed from the carboxylic group.



A study of substituted acetic acids shows that all substituents produce a retardation, two a still further retardation, and three substituents, e.g.  $\text{C}(\text{CH}_3)_3 \cdot \text{CO}_2\text{H}$ ,  $\text{CCl}_3 \cdot \text{CO}_2\text{H}$ , or  $\text{CPh}_3 \cdot \text{CO}_2\text{H}$ , produce acids which esterify very slowly.

The introduction of an olefine link into a fatty acid has a marked effect in lowering the velocity of esterification when in the  $\alpha\beta$ -position, in the  $\beta\gamma$ -position it produces a slight increase in the rate as compared with the corresponding fatty acid, and when further removed from the carboxylic group has no effect.

The introduction of methyl groups into methyl hydrogen succinates lowers the esterification constant, and similarly methyl and other groups retard esterification in the case of crotonic acid. A comparison of *cis* and *trans* pair of stereoisomerides shows that a substituent *cis* to the carboxylic group has a more marked effect than when *trans* to the group.

These phenomena are observed when the catalytic process of esterification is used. With the direct method of esterification polar effects are very marked; as a rule, the stronger the acid the more readily it reacts with an alcohol, thus oxalic and tartaric acids react with alcohol without an acid catalyst, and even trichloroacetic acid reacts with alcohol more readily than the unsubstituted acid.

Other methods for preparing esters, e.g. action of alkyl iodides on the silver salts of the acids or of alcohols on the acid chlorides, can be used even in the case of diortho-substituted benzoic acids.

This retardation or even complete inhibition of esterification is of practical value:

(1) In the separation of acids. By using the *Fischer-Speier* method the one acid can be completely converted into an ester, whereas a large part of the other acid can be recovered unchanged. It is a method which has been used for separating a mixture of an  $\alpha\beta$ -unsaturated acid with the isomeric  $\beta\gamma$ -acid.

(2) For confirming the structure of a given acid; thus an aromatic acid which is readily esterified by the usual process cannot have its substituents in the two ortho-positions (Chap. XXVI, C.).

With polycarboxylic aromatic acids the carboxylic groups which are not diortho-substituted are esterified, but those with two ortho-substituents are not, thus the *s*-tricarboxylic

acid gives a trimethyl ester, but the 1:2:3-tricarboxylic acid a dimethyl ester.

Steric hindrance is also observable in the naphthalene and anthracene series; thus 2-chloronaphthalene-1-carboxylic acid is not esterified, whereas the isomeric 1-chloro-2-carboxylic acid yields an ester as one of the *o*-positions has no substituent.

Similarly anthracene-9-carboxylic acid and 9-chloro-10-carboxylic acids do not yield esters, whereas the 1-carboxylic acid and the 2-chloro-3-carboxylic acid are readily esterified.

Steric inhibition has also been observed in the catalytic esterification of acids derived from heterocyclic systems, e.g. indole (*Auwers*, A., 1929, 467, 57).

Polar effects also are observable in catalytic esterification, and may strengthen the steric retardation or may lessen this according to the polar nature of the substituents present. Thus both trimethyl- and trichloro-acetic acids esterify very slowly, but the enormous difference between the two rates cannot be attributed to the difference in space-filling of the chloro and methyl groups, but is largely due to the electron-attracting (acylous) Cl atoms augmenting the steric effects, whereas the electron-repelling (basylous) methyl groups tend to diminish their effect (*Hinschlewood* and *Legard*; J. C. S., 1935, 537, 1588).

Steric retardation has been observed in the hydrolysis of aromatic esters by mineral acid and even in the hydrolysis of aromatic acyl chlorides, nitriles and acid amides, although in these latter cases polar effects play an important part. Steric hindrance has also been observed in the hydrolysis of substituted malonic esters and malonamides. Thus two ethyl groups in malonamide have a greater retarding effect than two methyl groups, and the *n*-propyl group has the same effect as two methyl groups. Similarly, triphenylacetamide,  $\text{CPh}_3 \cdot \text{CO} \cdot \text{NH}_2$ , dibenzylmethylacetamide, benzyldimethylacetamide, and methylphenylamino-phenylacetamide,  $\text{MePhN} \cdot \text{CHPh} \cdot \text{CO} \cdot \text{NH}_2$ , are difficult to hydrolyse.

The introduction of two *o*-methyl groups into acetanilide also produces a product extremely stable towards boiling hydrochloric acid.

Ortho-substituted benzonitriles are not readily saponified, but treatment with concentrated sulphuric acid converts them into acid amides which yield the corresponding acids by treatment with nitrous acid. The same nitriles cannot

undergo alcoholysis to esters (A., 1928, 467, 158), and similarly aromatic nitriles with ortho-substituents or aliphatic nitriles with several substituents in the  $\alpha$ -position do not yield iminoethers (Chap. VII, E and G).

Steric hindrance is extremely marked in the reaction between aromatic tertiary amines and alkyl iodides (formation of quaternary ammonium salts (Chap. XXI, D.). Fischer (B., 1900, 345, 1967) showed that the introduction of two ortho-substituents completely prevents the formation of an ammonium salt, and similarly diortho-substituted anilines do not yield alkylthiocarbimides with thiocarbonyl chloride (J. C. S., 1926, 3041). Alkyl groups in both ortho-positions in a dialkylarylamine prevent the formation of an oxide (Chap. XXI, C.) (Bamberger and Rudolf, B., 1906, 4285). The formation of a para nitroso derivative is also inhibited by the presence of two ortho-substituents (Cl or  $\text{CH}_3$ ) (Von Braun, B., 1918, 282), and the formation is also prevented by the presence of a tertiary alkyl group in  $\text{C}_6\text{H}_5\cdot\text{NR}\text{R}'$  (Hickinbotham, J. C. S., 1933, 946).

Many of the characteristic reactions of ketones exhibit steric retardation. Thus the ketone,  $\text{Me}\cdot\text{CO}\cdot\text{CMe}_3$ , yields only 5.6 per cent of bisulphite additive compound, whereas under similar conditions acetone gives a 60 per cent yield.

In the reaction of ketones with hydroxylamine and phenylhydrazine the accumulation of substituents around the carbonyl group or the presence of ortho-substituents in an aromatic ketone completely inhibits the formation of oximes and phenylhydrazones.

Substituents in the *p*-benzoquinone molecule retard oxime formation, the 2:6-dichloro compound forms a monoxime readily but a dioxime with great difficulty, and compounds with three or four substituents do not yield oximes.

Similar effects are observed in the formation of phenylhydrazones. A single ortho-substituent like picrylamino,  $\cdot\text{NHC}_6\text{H}_2(\text{NO}_2)_3$ , can completely prevent the formation of a phenylhydrazone, whereas in the para-position it has not the same effect.

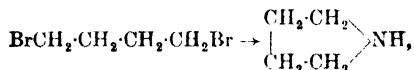
A comparison of ketonic acids  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CO}_2\text{H}$  with ketones  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3$  shows that ortho-substituents in the former have not the same inhibiting effects as in the latter.

Steric retardation is met with in the conversion of ketones to tertiary alcohols with the aid of Grignard reagents, with

compounds of the types (1)  $\text{CR}_3 \cdot \text{CO} \cdot \text{CHR}_2$  and (2)  $\text{CR}_3 \cdot \text{CO} \cdot \text{CR}_3$ ; the reaction is normal and no by-products are formed when  $\text{R} = \text{CH}_3$ . When  $\text{R} = \text{C}_2\text{H}_5$  the reaction proceeds less readily, but the  $\text{Pr}^n$  group has much the same effect as  $\text{Me}$ , whereas  $\text{Pr}^{\text{iso}}$  has a much greater retarding effect than  $\text{Et}$ . Compounds of type 1 react more readily than corresponding compounds of type 2 (B., 1937, 599).

The presence of several negative groups in iodobenzene, e.g. tetra- and pentachloro-iodo benzene, prevents the formation of iododichlorides (Chap. XIX).

1 : 4-Dibromo paraffins as a rule react with ammonia yielding cyclic bases, viz. the pyrrolidines,



whereas the compound  $o\text{-C}_6\text{H}_4(\text{CH}_2\text{Br})_2$  reacts in the same way as a 1 : 2-dibromo compound yielding  $o\text{-C}_6\text{H}_4(\text{CH}_2\text{NH}_2)_2$  (V. Braun, B., 1908, 2158).

Two *o*-substituents prevent the hydrolysis of phenacylpridinium salts with sodium hydroxide at  $20^\circ$ , whereas with *m*- and *p*-substituted compounds the reaction is markedly polar (B., 1937, 862).

Steric hindrance has also been noted with *Grignard* compounds (B., 1929, 62, 1379; C. R., 1932, 195, 252).

## XXXVII. AROMATIC SUBSTITUTION

*Hübner* (1875) and *Noelting* (1876) were the first to point out that certain aromatic compounds yield a mixture of *o*- and *p*-derivatives on nitration or sulphonation, whereas other compounds under similar treatment yield *m*-derivatives. An enormous amount of work has been done on substitution and on the isolation and estimation of the various products formed under slightly different conditions. *Hollemann's* researches (*Die direkte Einführung von Substituten*, 1910) prove that

although in many cases the main product is a mixture of *o*- and *p*-compounds, yet frequently a small amount of *m*-product is also formed, and that the conditions affect the relative proportions of isomers formed. At 0° benzoic acid yields 80.2 per cent of *m*-, 18.5 of *o*-, and only 1.3 of *p*-nitrobenzoic acid; at 30° nitrobenzene yields 91 per cent of *m*-, 8 of *o*- and 1 of *p*-dinitrobenzene. *Reese* (Chem. Rev., 1934, 55) gives a résumé of all the facts known with regard to the products formed by the halogenation, nitration and sulphonation of benzene compounds containing the following substituents: CO<sub>2</sub>H, NO<sub>2</sub>, SO<sub>3</sub>H, Me, OH, NH<sub>2</sub>, Cl, Br and I, and under varying conditions of concentration, temperature and pressure. The products isolated may not be the initial products formed, but may be due to the isomerization of these. Thus in the sulphonation of benzoic acid an intermediate product is apparently the *o*-sulphonic acid which, under the conditions of the experiment is transformed into the *m*-acid (J. A. C. S., 1932, 2009). In the nitration of benzene-sulphonic acid the main product is the *m*-compound, but a rise of temperature from 25° to 55° increases the proportion of *o*-, and at 150°–160° the proportions of *m*- and *o*-compounds are 40 and 27.4 per cent. *Reese* gives the results of nitrating benzene derivatives containing 55 different groups, and points out that the reactions fall into 3 categories: (1) Where practically only 1 product is formed. (2) Where roughly equal amounts of two are formed to the exclusion of the 3rd. (3) Where all 3 isomers are formed. Whenever the percentage of either *m*- or *p*- preponderates the principal secondary product is always the *o*-compound, hence presumably a substituent is either *o* and *p* or *o* and *m* directing.

If, on the other hand, the *o*-compound is the chief product, the secondary product is always the *p*-, and never the *m*-compound. An extremely interesting example of the effect of conditions on nitration is met with in the case of benzaldehyde which forms the definite compound, C<sub>6</sub>H<sub>5</sub>·CHO, HNO<sub>3</sub>, and this on treatment with H<sub>2</sub>SO<sub>4</sub> + HNO<sub>3</sub> gives the *m*-nitrobenzaldehyde, but with Ac<sub>2</sub>O + HNO<sub>3</sub> the *p*-compound, accompanied in both cases with traces of the *o*-isomer (Z. angew., 1932, 580). *Ainley* and *Challenger* (J. C. S., 1930, 2171), by nitrating phenylboric acid, obtained 72 per cent of *m*-, and 28 of mixed *o*- and *p*-compounds, whereas *Seaman* and *Johnson* (J. A. C. S., 1931, 711), by using a mixture of

$\text{Ac}_2\text{O}$  and fuming nitric acid, obtain a 65 per cent yield made up of 95 ortho and 5 para. Toluene and *tert*-butylchloride with  $\text{AlCl}_3$  give *m*- and *p*-*tert*-butyltoluenes in the ratio 70 : 30, although the group is usually regarded as para-orientating (J. C. S., 1930, 2231).

It is possible that reversed directive effects are due to a difference in the mechanism of the reaction. In some cases the reaction may be direct substitution, in others an additive compound may be first formed (*Blanksma*, Rec. trav., 1902, 281; 1904, 202).

As a rule an increase in temperature increases the proportion of *o*-compound, especially in nitrations. In sulphonations the reverse is true, the proportion of *p*- increases with the temperature, due to the fact that the *o*- changes to the *p*- at the higher temperatures.

Several empirical rules have been formulated embodying the *o*-, *p*- and *m*-orientating effects of different substituents.

The *Crum-Brown-Gibson* rule (J. C. S., 1892, 367) states that whenever a benzene compound  $\text{C}_6\text{H}_5\text{X}$  contains a group X whose hydride is readily oxidizable by a one-stage process to  $\text{X}\cdot\text{OH}$ , then  $\text{C}_6\text{H}_5\text{X}$  gives a meta disubstituted derivative, whereas if  $\text{HX}$  is not directly oxidizable to  $\text{X}\cdot\text{OH}$  the product is a mixture of *o*- and *p*-compounds. This rule has been modified by *Waters* to read as follows: "If the group X is more stable in its compounds with H than with OH, e.g. Cl ( $\text{HCl}$  and  $\text{HOCl}$ ),  $\text{NH}_2$  ( $\text{NH}_3$  and  $\text{NH}_2\text{OH}$ ), OH ( $\text{H}\cdot\text{OH}$  and  $\text{OH}\cdot\text{OH}$ ), then it is *o*- and *p*-directing, but if the reverse is true, e.g.  $\text{NO}_2$  ( $\text{HO}\cdot\text{NO}_2$  and  $\text{H}\cdot\text{NO}_2$ ),  $\text{CO}_2\text{H}$  ( $\text{OH}\cdot\text{CO}\cdot\text{OH}$  and  $\text{H}\cdot\text{CO}\cdot\text{OH}$ ), then X is *m*-directing" (Physical Aspects of Organic Chemistry, Chap. XVI, 1B), and from this it is clear that the polar characteristic of the group X is the determining factor. A rule propounded by *Hammick* and *Illingworth* (J. C. S., 1930, 2358) reads as follows: "If in the benzene derivative  $\text{C}_6\text{H}_5\cdot\text{XY}$ , Y is in a higher group of the periodic table than X, or if, being in the same group, Y is of lower atomic weight than X, e.g.  $\text{X} = \text{C}$ ,  $\text{Y} = \text{O}$ , or  $\text{X} = \text{N}$ ,  $\text{Y} = \text{O}$ , then a second atom or group of atoms that enters the nucleus will do so in the *m*-position to the group  $\cdot\text{XY}$ ." In all other cases, e.g.  $\text{X} = \text{N}$ ,  $\text{Y} = \text{H}$ , or  $\text{X} = \text{O}$ ,  $\text{Y} = \text{H}$ , including that in which  $\cdot\text{XY}$  is a single atom, the second group goes to the *o*- and *p*-positions. The effect of ionic charges on XY is given by the statement that a + charge directs *m*- and a - charge *o*- and *p*-substitution.

*Sutton* (P. Roy. S., 1931, **133A**, 668) points out a relationship between the directive influence of a substituent X and the sign of the difference between the dipole moments of aryl X and aliphyl X. When the difference is positive, X is *o*- and *p*-directive, but when negative *m*-directive (cf. also *Groves and Sugden*, J. C. S., 1935, 973, who used the vapour phase as compared with *Sutton's* solutions in benzene). The rule holds good for CH<sub>3</sub>, F, Cl, Br, I, CN, NO<sub>2</sub>, CO·CH<sub>3</sub>, combined with C<sub>6</sub>H<sub>5</sub> as the aryl and tertiary butyl as the aliphyl group.

When two or more substituents are present it is not always easy to predict the position which a new group, e.g. NO<sub>2</sub>, Br, will assume. The groups present may have opposing effects on the entrant, or they may have a cumulative effect. In such cases *Hollemann's* list of relative magnitudes of the directing powers of substituents is of value. These values are largely based on the relative speeds of nitration at 0° with fuming nitric acid.

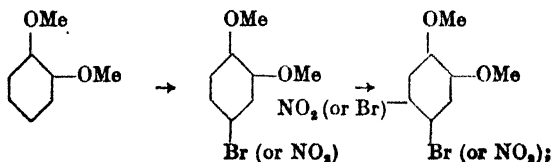
*o*- and *p*-Directing groups in decreasing order are OH, NH<sub>2</sub>, NR<sub>2</sub>, NHAc, Cl, Br, CH<sub>3</sub>, alkyl, I.

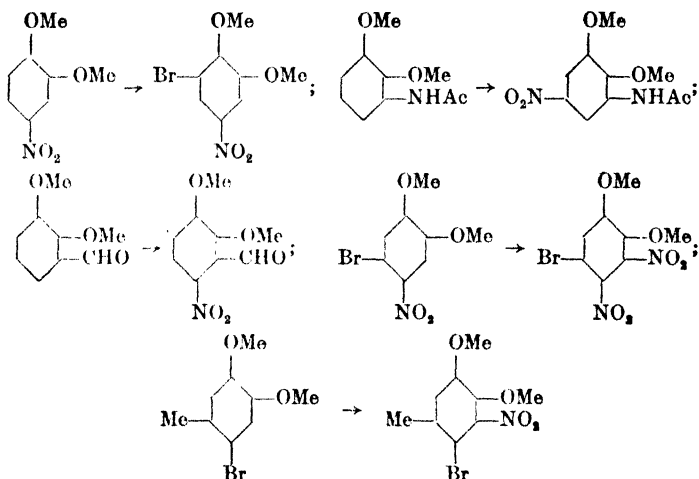
*m*-Directing groups in decreasing order are CO<sub>2</sub>H, SO<sub>3</sub>H, NO<sub>2</sub>, and all are much less effective than the *o*- and *p*-directing groups. In fact, compounds with *o*- and *p*-orientating groups are more readily substituted than benzene itself, whereas those with *m*-orientating groups are much more difficult to nitrate, sulphonate or halogenate than benzene. Compare *Vörlander*, B., 1919, 263, who gives the following classification:

1. Meta-orientating: SO<sub>3</sub>H, NO<sub>2</sub>, CHO, CO<sub>2</sub>H, CO<sub>2</sub>R, CONH<sub>2</sub>, COR, CO·CO<sub>2</sub>H, CN, CCl<sub>3</sub>, NH<sub>3</sub>X, NR<sub>3</sub>X.

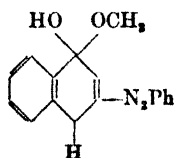
2. Ortho- and para-orientating: OH, OR, OAc, NH<sub>2</sub>, NHR, NR<sub>2</sub>, NHAc, N:N, CH<sub>3</sub> and aliphyls, CH<sub>2</sub>Cl, CH<sub>2</sub>·O·NO<sub>2</sub>, CH<sub>2</sub>·SO<sub>3</sub>H, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>CN, CH<sub>2</sub>·CO<sub>2</sub>H, CH<sub>2</sub>·CH<sub>2</sub>·CO<sub>2</sub>H, CH:CH·CO<sub>2</sub>H, CH:CH·NO<sub>2</sub>, C:C·CO<sub>2</sub>H, C<sub>6</sub>H<sub>5</sub>.

(For substitution in veratrole (1:2-dimethoxybenzene) cf. *Jones and Robinson*, J. C. S., 1917, 903.)





Both *Armstrong* and *Hollemann* have suggested the formation of additive compounds by the addition of the reagent to double bonds in the aromatic compound, and in *o*-substitution this addition occurs in the 1 : 2-positions and in *p*-substitution at the 1 : 4-positions of the conjugated system, and followed in the case of nitration by the elimination of H<sub>2</sub>O. In a few cases actual additive products of an olefine and nitric acid, OH·NO<sub>2</sub>, have been isolated, and anthracene gives an additive compound with nitric acid. Similarly, it is possible that in the *Friedel-Crafts* reaction addition occurs at a double bond followed by elimination of hydrogen chloride, and also in the coupling of a phenol or amine with a diazonium salt (Chap. XXII, A.) the formation of an additive compound is highly probable as, when a phenolic ether is used, some replacement of OMe by OH occurs, e.g. α-naphthol methyl ether with a diazonium hydroxide gives both 1 : 4-C<sub>10</sub>H<sub>6</sub>(OMe)(N<sub>2</sub>Ph) and 1 : 4-C<sub>10</sub>H<sub>6</sub>(OH)(N<sub>2</sub>Ph), which are probably formed by the elimination of H·OH and Me·OH respectively from the additive compound:





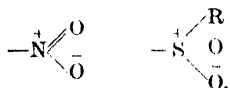
In a previous chapter (XXXV) reagents have been classified into the two groups cationoid and anionoid, and in aromatic substitutions practically all the reagents used, e.g. halogens, nitric and sulphuric acids, belong to the former group, and hence reactions will occur and have orientations depending on the relative electron densities of the different carbon atoms of the nucleus, those with the greater density being the more reactive. These densities are influenced by inductive and tautomeric (electromeric) effects in the molecules, i.e. in the case of substituted benzenes by the electron-attracting  $+I$ ,  $+T$  or electron-repulsing effect of the  $-I$ ,  $-T$  substituents. These effects will be the most marked on neighbouring C, i.e. *ortho* carbon atom, and can be transmitted along the conjugate system of the benzene ring to the *para* C atom. Thus the  $\bar{O}$  ion present in the alkali salt of a phenol will have the strongest electron-repulsing effect and hence will produce an appreciable increase in electron density on the *ortho* and *para* carbon atoms, and therefore will induce marked *o*- and *p*-orientation in processes of nitration, sulphonation and halogenation.

A cation  $\overset{+}{N}Me_3$  present in the ring will produce strong electron attraction, and hence tend to withdraw electrons from the nucleus more particularly from the *o*- and *p*-C atoms, and hence the *meta*-positions will be those more readily attacked, but then only slowly. Other onium ions, e.g. sulphonium, iodonium, phosphonium, arsonium, have similar *m*-directing effects.

An increase in the distance of such an ion from the nucleus by the interposition of  $CH_2$  groups produces marked results on the amounts of *m*- or *o*- and *p*-compounds formed; thus on nitration  $C_6H_5\cdot\overset{+}{N}Me_3$  yields 100,  $C_6H_5\cdot CH_2\cdot\overset{+}{N}Me_3$  88, and  $C_6H_5\cdot CH_2\cdot CH_2\cdot\overset{+}{N}Me_3$  only 19 per cent of *m*-derivative, thus illustrating the diminution of the inductive effect through a chain of carbon atoms. Inductive effects are also well marked in the series of compounds  $C_6H_5\cdot CH_2X$  on nitration; the percentage of *m*-nitro-compound increases in the order H 4, Br 7, Cl 12, F 18, and  $NO_2$  48.

Actual experiment shows that *op*-effects diminish in the order OH,  $NH_2$ , halogen, methyl, and *m*-directing effects in the order  $CO_2H$ ,  $SO_3H$ ,  $NO_2$ .

Co-ordinate or semi-polar links, e.g.  $-\text{NO}_2$  and  $-\text{SO}_2\text{R}$  are highly polar, e.g.:



with a positively charged atom directly attached to the nucleus, and hence *m*-orientation occurs, but the interposition of  $\text{CH}_2$  between the  $\text{NO}_2$  group and the nucleus diminishes the *m*-orientating influence of the nitro-group.

The presence of an ethylene link in the substituent, e.g. styrene  $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}_2$  and also diphenyl where the 6 double bonds are conjugate, leads to increased activity and distinct *op*-orientating effects which persists in such compounds as  $\text{PhCH}:\text{CHNO}_2$ ,  $\text{PhCH}:\text{C}(\text{CN})\cdot\text{CO}_2\text{Et}$ ,  $\text{PhCH}:\text{CH}\cdot\text{C}_6\text{H}_3(\text{NO}_2)_2$ , &c., which might function as cationoid systems. (For diphenyl derivatives cf. J. C. S., 1926, 476, 2041; 1930, 1158.)

With a hetero atom O, S, N, halogen, attached to the nucleus a heteroenoid conjugated system (Chap. LI, C2) is formed, and compounds like phenol, anisole, aniline, chlorobenzene are more readily brominated or nitrated than benzene, and almost exclusively in the *o*- *p*-positions, and the reactivity of groups diminishes in the order  $\text{RN}^--$ ,  $\text{O}^--$ ,  $\text{R}_2\text{N}^--$ ,  $\text{RO}^--$ , I, Cl, and in general is greater the greater the proton affinity of the group.

Amongst derivatives of amines the order is  $\text{NR}_2 > \text{NH}_2 > \text{NHAc}$ , and amongst phenols  $\text{O}^- > \text{OH} > \text{OAc}$ .

Phenols and amines contain such powerful heteroenoid systems that they are attacked by even feeble cationoid reagents like nitrous acid and diazonium salts ( $\text{N}_2\text{Ph}$ ).

Some of the most accurate measurements of the chlorination of phenols have been made by *Soper* and *Smith* (J. C. S., 1926, 1582), using the hypochlorous acid method in acid or alkaline solution, and the results show that the reaction is between phenoxide anions and hypochlorous acid molecules, and for different phenols the product (velocity of chlorination  $\times$  ionization constant of phenol) is practically constant, indicating that the anion derived from the more acidic phenol (nitro, &c.) are less reactive. Experiments with compounds  $\text{R}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{X}$ , where R represents alkyl group Me, Et, Pr, Bu<sup>n</sup>,

$\text{CH}_2\text{Ph}$ ,  $\text{Ac}$ , and  $\text{X}$  represents  $p\text{-CO}_2\text{H}$ ,  $p\text{-NO}_2$ ,  $p\text{-Cl}$ ,  $o\text{-Cl}$ , show that the rate of chlorination for a given alkyl compound is independent of the second substituent  $\text{X}$ , i.e. the electromeric activation by the particular group  $\text{R}\cdot\text{O}-$  is independent of other substituents, and similarly it has been shown that the inductive effect ( $+I$ ) of a group  $\text{X}$  affects the velocity by a constant amount.

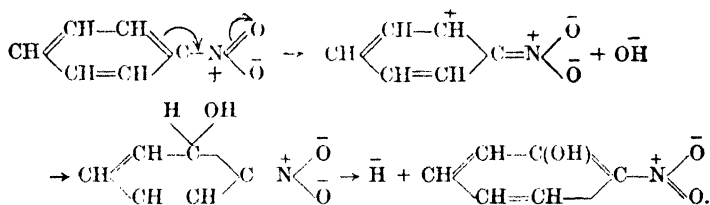
Generally speaking, a substituent which induces a positive dipole in an aromatic ring, e.g.  $\text{CH}_3$ ,  $\text{OH}$ ,  $\text{NH}_2$ ,  $\text{Cl}$ ,  $\text{Br}$ ,  $\text{I}$ ,  $\text{CH}_2\text{Cl}$ , has  $o$ - and  $p$ -directing effects and a group which induces a negative dipole, e.g.  $\text{CCl}_3$ ,  $\text{COCH}_3$ ,  $\text{CHO}$ ,  $\text{CN}$ ,  $\text{NO}_2$ , a meta-directing effect (*Sutton*, p. 636).

A phenomenon frequently observed during substitution is the replacement of a group already present by the substituting reagent. A well-known example is the bromination of sulphanilic acid. If care is taken the 2:6-dibromo-sulphanilic acid, with the two bromines ortho to the  $\text{NH}_2$  group and the  $\text{SO}_3\text{H}$  para to the  $\text{NH}_2$ , is formed; but with a slight excess of bromine the product is *s*-tribromaniline, the  $\text{SO}_3\text{H}$  group being replaced by  $\text{Br}$ . (For summary of such replacements cf. *Sudborough and Lakhumalane*, J. I. I. S., 1914, 133.) Groups which are replaced by  $\text{Br}$ ,  $\text{NO}_2$  are  $\text{SO}_3\text{H}$ ,  $\text{CO}_2\text{H}$ ,  $\text{CHO}$ ,  $\text{CO}\cdot\text{CH}_3$ , i.e.  $m$ -directing substituents, and halogen by nitro-groups, but always in ortho- or para-positions to an  $\text{OH}$  or  $\text{NH}_2$  group, and *Robinson* claims (*loc. cit.* p. 71) that such replacements are explicable from the electronic point of view.

## Cationoid Reactions of Aromatic Compounds

As already pointed out (Chap. XXXV) in the great majority of reactions benzene derivatives behave as anionoid compounds and readily react with cationoid reagents. By introducing suitable groups the aromatic compound can be given cationoid properties, and will then react with anionoid reagents. A nitro-group in benzene produces this effect, as a cationoid conjugate system is developed and a tendency to attract electrons from the benzene ring. Hence the hydrogen atoms,  $o$ - and  $p$ - to the nitro-groups should be reactive towards

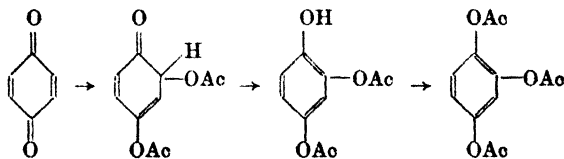
anionoid reagents. A good example is the action of strong alkalis ( $\text{OH}^-$ ) on nitro-benzene to form *o*-nitro-phenol.



With more than one nitro-group present, e.g. *m*-dinitrobenzene, the reaction takes place more readily and the H ortho to both  $\text{NO}_2$  groups is readily replaced by CN.

Other meta-directing substituents such as CO have the same effect. The conversion of anthraquinone into alizarin by fusion with potash is another example, and as a rule the elimination of H is facilitated by the addition of an oxidizing agent. Here the carbonyl group is conjugated with the benzene rings and the catio-enoid system ( $>\text{C}=\text{C}-\text{C}=\text{O}$ ) formed (p. 837).

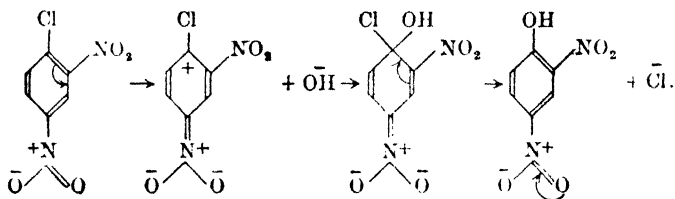
The formation of 1:2:4-triacetoxy benzene,  $\text{C}_6\text{H}_3(\text{OAc})_3$ , by the action of acetic anhydride and sulphuric acid on benzoquinone is an example. The reaction consists in the addition of Ac to 1 and OAc to 4 in the catio-enoid system (numbering see above), the subsequent enolization of the additive product and the acetylation of the resulting enol:



Substituents in the benzoquinone molecule have a pronounced effect. Thus methoxyquinone is more reactive to acetylation than quinone as the methoxy group produces a more or less neutralized system with the one catio-enoid group  $\cdot\text{C}(\text{OMe})\text{:CH}\cdot\text{C}=\text{O}$ , and hence renders the other group  $\cdot\text{CH}\text{:CH}\cdot\text{C}:\text{O}$  more reactive. The 2:5-dimethoxyquinone, on the other hand, does not react with the acetylating reagent as both catio-enoid systems are neutralized. Alkyl groups

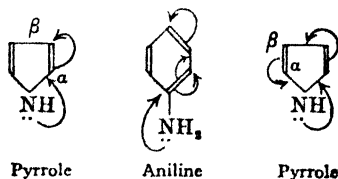
react somewhat similarly but are weaker, and their effect increases in the order Me, Et, Pr(iso).

The substitution of H by OH or Ac does not, as a rule, take place readily, as the H is eliminated as the unstable anion  $\bar{H}$ , and occurs only when an oxidizing agent is present to discharge this. If, however, a substituent is present which can form a stable anion, e.g.  $\bar{Cl}$ ,  $\bar{NO}_2$ , this can be readily eliminated from a catio-enoid system. Thus the chlorine in 2:4-dinitrochlorobenzene, i.e. *ortho* to one  $NO_2$  group and *para* to the other, is remarkably reactive and can be replaced by OH, CN,  $NH_2$ , &c., and with *s*-trinitrochlorobenzene the reaction takes place still more readily so that the compound possesses the properties of an acid chloride and is known as picryl chloride:



## Substitution in Heterocyclic Compounds

Pyrrole (Chap. XL) is extremely readily substituted by cationoid reagents, e.g. with halogens it readily yields tetra-halogenated compounds. According to *Robinson* the  $\beta$ -position is analogous to the *ortho*-positions, and the  $\alpha$ -position to the *para*-position in aniline or phenol.



Pyridine and quinoline are not readily attacked by cationoid reagents, and in this respect resemble nitrobenzene; on the other hand, they are substituted by anionoid reagents,

e.g. pyridine and sodamide yield  $\alpha$ -aminopyridine, and also the formation of *pseudo* bases by the action of alkali on a quinoline salt is a case of anionoid substitution ( $\bar{\text{O}}\text{H}$ ) and subsequent phototropic change.

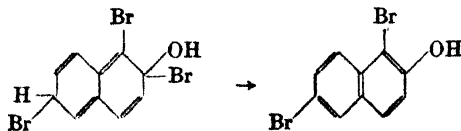
## Substitution in Condensed Benzene Systems

Naphthalene at low temperatures usually yields  $\alpha$ -substituted derivatives, sometimes preceded by 1:4-addition, e.g. chlorine gives naphthalene dichloride which by loss of HCl yields the more stable  $\alpha$ -chloro-naphthalene.

If an OH or  $\text{NH}_2$  or  $\text{CH}_3$  group is already present then the second substituent Cl,  $\text{NO}_2$ ,  $\text{SO}_3\text{H}$ , &c., will enter the same ring as the OH or  $\text{NH}_2$  group, and this latter group will exert *o*- or *p*-directing influences. Thus  $\alpha$ -naphthol or  $\alpha$ -naphthylamine will yield both 2 and 4 substituted products, and  $\beta$ -naphthol or  $\beta$ -naphthylamine will yield only 1-substituted derivatives but not a 3-substituted compound. With groups other than OH and  $\text{NH}_2$  present the substitution occurs in the second ring.

When a substituent enters the second ring it usually takes up the  $\alpha$ -positions, i.e. 5 or 8, independently of the polar nature of the substituents already present in the first ring. This may be due to the polar action of the one conjugated system on the other. When, however, an *o*-, *p*-directing substituent is present in position 2, then the second group often takes up position 6. Thus in the nitration of 2-chloro-, bromo- or alkyloxy-naphthalenes the products are usually 2:6:8-trisubstituted derivatives, and the same holds good for the sulfonation of  $\beta$ -naphthol or  $\beta$ -naphthylamine.

In brominating  $\beta$ -naphthol quinonoid compounds are formed by direct addition; these contain active bromine atoms, but on the loss of HBr yield a bromo- $\beta$ -naphthol:



(A., 1930, 484, 245).

**Diphenyl.**—In contrast to naphthalene electromeric changes do not tend to pass from ring to ring, although the molecule presents a complete conjugated system. All compounds of the type  $C_6H_5 \cdot C_6H_4X$ , whatever  $X$  may be, yield derivatives substituted in the *o*- or *p*-position to the bond linking the two phenyl groups. Thus all three mono-nitro diphenyls on further nitration yield a 4' or a 2' product. If an  $NH_2$  or  $OH$  group is present this produces *o*- or *p*-substitution in the same ring; this 4-amino-diphenyl gives as first product the 3-substituted product and 3-amino-diphenyl gives a 4-substitution product. A nitro-group on the other hand gives rise to a product substituted in the second ring.

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### XXXVIII. MOLECULAR REARRANGEMENT \*

Numerous examples have already been given of the migration of a radical or atom within a molecule. The simplest type of such migration is met with in racemization (p. 293, Chap. X), where the migrating radical is attached, in the initial and in the final compound, to the same carbon atom, but has changed its position relative to the other groups attached to this central atom. Analogous to this is the *Walden* inversion, where starting with the *d* (or *l*) form of a given compound it is possible by a series of reactions to obtain the corresponding antipodes (Chap. LXXI, I4).

In other types dealt with in this chapter the radical no longer remains attached to the same atom, but migrates and becomes attached to an adjacent atom or even to one further removed.

As a rule these rearrangements are not reversible, and in this respect differ from tautomeric changes (Chap. LIII). When the rearrangement takes place readily it is quite possible that the migration occurs during the preparation of a compound, so that a structure deduced from that of the original compound may be incorrect.

The rearrangement always occurs with a decrease of free energy, and in some cases intermediate compounds can be

\* C. W. Porter, *Molecular Rearrangement*, New York, 1928.

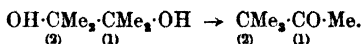
isolated. These rearrangements are due to the migration of one or more radicals, and it is customary to classify rearrangements into the following types:

- A. Migration from C to C.
- B. Migration from N to C.
- C. Migration from C to N.
- D. Migration from O to C.
- E. Migration from O to N or N to N.
- F. Migration from I to C.

## A. Migration from C to C

### 1. Pinacone-pinacolin transformation or Pinacol-pinacolone transformation.\*

This is one of the commonest of the C to C changes, and occurs when an  $\alpha\beta$ -glycol (pinacol), obtained, together with a secondary alcohol, by the reduction of a ketone, is warmed with sulphuric acid when water is eliminated (p. 223):



It is clear that a methyl group migrates from carbon No. 1 to carbon No. 2. The reaction is a general one for all compounds of this type, and with pinacols containing two different alkyl groups it is found that one is more mobile than the other. *Tiffenau* (1925) represented the reaction as the removal of a molecule of water, the formation of a radical with two free valencies, and the migration of a methyl group in order to satisfy the free valencies.

In all probability the reaction is ionic as it occurs in the presence of an electrolyte, viz. sulphuric acid. The glycol forms a mono-sulphate which ionizes to  $\text{HSO}_4$  and  $\overset{+}{\text{CMe}_2}\cdot\underset{(1)}{\text{CMe}_2}\cdot\text{OH}$ .

By the wandering of a negative methyl group from C(1) to C(2) the product  $\text{CMe}_3\cdot\overset{+}{\text{CMe}}\cdot\text{OH}$  is formed, and this by the loss of a proton gives  $\text{CMe}_3\cdot\overset{+}{\text{CMe}}\cdot\bar{\text{O}}$  or  $\text{CMe}_3\cdot\text{CMe}:\text{O}$  (cf. *Kermak and Robinson*, J. C. S., 1922, 427).

\* The names pinacone and pinacolin are confusing as the former is a dihydric alcohol and the latter a ketone, hence the names pinacol and pinacolone have been suggested.



Analogous to the above reaction is the conversion of the di-secondary alcohol, hydrobenzoin (Chap. XXIX), into diphenylacetaldehyde under the influence of sulphuric acid:

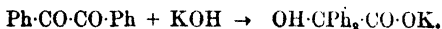


and intermediate between the pinacol and hydrobenzoin transformations is the reaction of the secondary-tertiary-glycol,  $\text{OH}\cdot\text{C}(\text{Et})_2\cdot\text{CHPh}\cdot\text{OH}$ , which with hot dilute sulphuric acid gives  $\text{CPhEt}_2\cdot\text{CH}:\text{O}$ , and with cold concentrated sulphuric acid gives  $\text{EtCO}\cdot\text{CH}(\text{Et})\text{Ph}$ .

An analogous migration occurs in the reaction of an  $\alpha\beta$ -aminoalcohol with nitrous acid (*M'Kenzie*, J. C. S., 1924, 2105):



## 2. Benzil-benzilic acid transformation (Chap. XXIX):



This occurs in the presence of hot dilute alkali and may be due to the addition of  $\text{OH}$  to the  $\text{CO}$  group.

**3. Wagner-Meerwein Rearrangement.**—The classical example is the conversion of pinene into bornyl chloride (Terpenes, Chap. LVII, C.). The first stage is the addition of  $\text{HCl}$  to pinene forming pinene hydrochloride, the ionization into  $\text{Cl}^-$  and the unstable cation which undergoes change to the more stable bornyl system by a C to C change resulting in the formation of two 5-carbon rings in place of the original 4 C and 6 C rings (*Meerwein*, A., 1927, 453, 16).

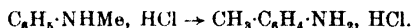
Similarly esters of camphene hydrate give isobornyl esters.

**4. Isomerization of Aromatic Sulphonic Acids.**—The product of sulphonation of an aromatic hydrocarbon varies with the temperature; thus naphthalene at temperatures below  $80^\circ$  yields as chief product the  $\alpha$ -sulphonic, whereas at  $160^\circ$  the  $\beta$ -isomeride is mainly formed, and on heating the  $\alpha$ -acid with concentrated sulphuric acid a mixture of  $\alpha$ - and  $\beta$ -acids is obtained. Similarly, the 2:7-disulphonic acid can be converted into the 2:6-isomeride, and in the case of sulphonic acids derived from  $\alpha$ - and  $\beta$ -naphthylamines there is a tendency for the acid group to migrate from the  $\alpha$ - to the  $\beta$ -position (*Green and Vakil*, J. C. S., 1918, 35).

In all probability this is not a direct migration, an intramolecular reaction, but is due to the elimination of  $\cdot\text{SO}_3\text{H}$  of the  $\alpha$ -compound and at the higher temperature the sulphonation of the  $\beta$ -position.

## B. Migration from N to C

1. **Hofmann transformation of the hydrochlorides of aliphyl-arylamines:**



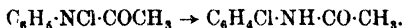
When the hydrochloride is heated at  $300^\circ$  the aliphyl group migrates from the nitrogen of the side chain to the *o*- or *p*-carbon atom of the nucleus (Chap. XXI, A.), and in many cases the same products are formed by heating the primary aryl-amine hydrochloride with methyl alcohol under pressure at  $300^\circ$ .

2. **Migration of an acyl group from a diacylated aromatic amine into the nucleus under the influence of acids:**

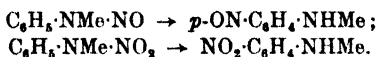


3. **Conversion of phenylhydroxylamines to *p*-hydroxy amines** under the influence of mineral acids (Chap. XXII, C.).

4. **The migration of halogen from N in a N-chloro acetanilide into the nucleus** (cf. p. 433):



5. **The migration of a nitroso group from a nitrosoaliphyl-arylamine or of a nitro-group from a nitroaliphylarylamine** by heating with hydrochloric acid (Chap. XXI, B.):

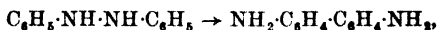


6. **The rearrangement of a diazoamino compound to an amino-azo derivative by aid of hydrochloric acid:**



(Chap. XXII, B.).

**7. The benzidine rearrangement of hydrazobenzene (Chap. XXII, C2):**



a reaction which takes place in the presence of strong acids, the product being a *pp'*-diaminodiphenyl (benzidine).

**8. Steven's rearrangement of quaternary ammonium salts.**

In all these cases of the wandering of a radical from attachment to a side chain N to an *o*- or *p*-carbon atom of the nucleus it is postulated that a cation  $\text{CH}_3^+$ ,  $\text{OH}^+$ ,  $\text{Cl}^+$ ,  $\text{Bz}^+$ , &c., is formed, probably with an extremely short life, the residual benzene anion undergoes isomeric change resulting in the *o*- and *p*-carbon atoms having strong anionic properties; the transient cation can then react with the activated *o*- and *p*-carbon atom or can, in some cases, act with the reagent.

Thus in type 4 the  $\text{Cl}^+$  reacts with the  $\text{HCl}$  or  $\bar{\text{Cl}}$ , forming molecular chlorine which can be shown to be present, and this chlorinates the amine (non-reversible) or reforms the chloro-amine (reversible) (*Orton* and co-workers, 1911-28). The reaction is of value as the concentration of the chlorine is low and more is formed as it is used up, and hence phenols and amines, which cannot be chlorinated in the usual manner, can be readily chlorinated by using the N-chloramine and hydrochloric acid. Decomposition of the chloro-compound also takes place readily in glacial acetic acid as the acid can liberate  $\text{HCl}$  from the chloro-compound.

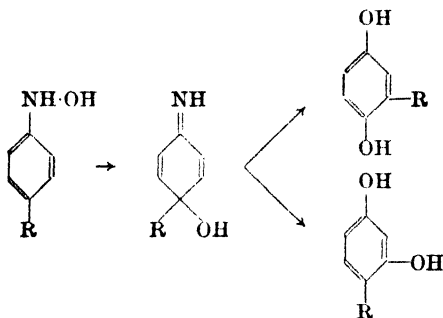
In reaction 5 there is no indication of the  $\text{NO}_2$  reacting with the reagent forming a nitrating agent, so that the reaction is probably intramolecular and hence different from reaction 4 which is intermolecular.

In reaction 1  $\text{CH}_3^+$  separates from the cation  $\text{C}_6\text{H}_5\cdot\text{NH}_2\cdot\text{CH}_3^+$ , leaving a ring activated in the *o*- and *p*-positions and strongly anionic, so that it reacts immediately with the  $\text{CH}_3^+$  cation.

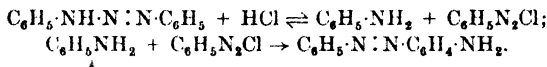
In reaction 3 the cation  $\text{OH}^+$  is formed, and the anionic nucleus by electromeric change becomes activated and the *p*-position reacts with the  $\text{OH}^+$  forming *p*-amino-phenol.

With a *p*-alkylated hydroxylamine a quinole is first formed,

and from this under the influence of dilute alkali or dilute sulphuric acid the alkyl migrates, whereas alcoholic sulphuric acid causes a migration of the OH group:

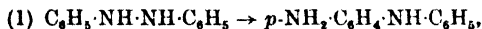


In reaction 6 a fission of the diazoamino compound into primary amine and diazonium salt occurs (reversible) and these then react (irreversible) to give the amino-azo compound. The reaction is of the intermolecular type:

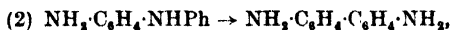


The formation of the diazonium salt is proved by the fact that, in the presence of dimethylaniline, hydrochloric acid decomposes the diazoamino compound yielding *p*-dimethyl-amino-azo-benzene,  $\text{NMe}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{N}\cdot\text{C}_6\text{H}_5$ .

Reaction 7 is complex and consists of two migrations:



viz. the migration of  $\cdot\text{NHPh}$  to a *para*-position;

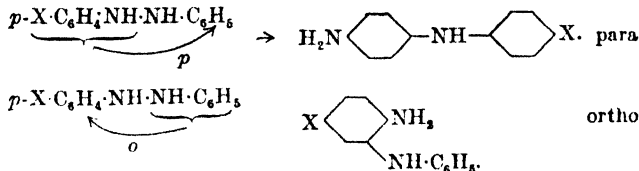


viz. the wandering of  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot$  to the *p'*-position.

A certain amount of ortho migration also occurs as 2 : 4'-diaminodiphenyl accompanies the benzidine (4 : 4'-diamino).

When a *para* substituent is present in the original hydrazo-

benzene only the first migration occurs, and the product is a para- or ortho-semidine:



(Cf. *Jacobson*, A., 1922, 428, 76.)

The rearrangement of a mixture of 2:2'-dimethoxy- and 2:2'-diethoxy-hydrazobenzene in the same solution yields only the two products 3:3'-dimethoxy- and 3:3'-diethoxy-4:4'-diaminodiphenyl; none of the mixed product 3-methoxy-3'-ethoxydiaminodiphenyl is formed, indicating that the reaction is purely intramolecular.

In reaction 8, the transformation of a quaternary ammonium salt, a benzyl group attached to N is found to migrate to an adjacent C atom under the influence of alkali hydroxides or alkoxides, e.g.  $\text{R-CH}_2\text{NR}'\text{Me}_2 \rightarrow \text{R-CHR}'\text{NMe}_2$ , where  $\text{R}'$  = benzyl (*Stevens*, J. C. S., 1928-32). The migration has been observed in cases where  $\text{R}$  = acetyl, benzoyl, substituted benzoyl, phenyl or vinyl, and  $\text{R}'$  = benzyl, substituted benzyl,  $\alpha$ -phenylethyl, benzhydryl, 9-fluorenyl or phenacyl. The reaction appears to be intramolecular, and probably an extremely transient  $\bar{\text{R}}'$  ion is formed.

A similar migration occurs in sulphonium compounds, but not in the corresponding oxonium salts (*ibid.* 1932, 69).

### C. Migration from C to N

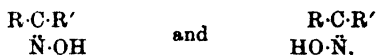
The most carefully studied reaction of this type is:

#### 1. The Beckmann Transformation of Oximes (Chem. Rev., 1933, 215).

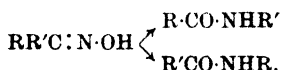
Oximes derived from ketones or the N-ethers of aldoximes under the influence of  $\text{PCl}_5$ ,  $\text{POCl}_3$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{HCl}$ ,  $\text{AcCl}$ ,  $\text{Ph-SO}_2\text{Cl}$ , and even  $\text{SbCl}_5$  pass into acid amides (*Beckmann*, 1886):



An unsymmetrical ketone,  $R \cdot CO \cdot R'$ , gives two stereo-isomeric oximes,

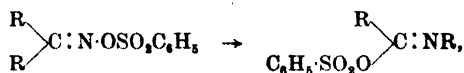


and each yields a characteristic amide under the above treatment:



*Hantzsch* (B., 1891, 13, 51) concluded that the transformation consists in the exchange of the OH group of the oxime with the alkyl group in the *cis* position, and based on this he deduced the configurations of the oximes from the actual acid amide formed by the *Beckmann* transformation. These configurations have been proved to be incorrect by *Meisenheimer* from a study of the relationship of the oximes to cyclic compounds, e.g. *iso*-oxazoles (cf. Chap. L, C1), and it is now generally accepted that in the transformation *trans* and not *cis* exchange takes place. *Mills* (B. A. Rep., 1932) points out that *trans* migration in oximes can take place more readily than *cis* migration as the latter would be impeded by the N atom.

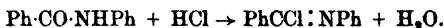
*Mechanism of the Reaction.*—As the reagents producing the change are largely of an acidic character, it was suggested by *Stieglitz* and also by *Lachman* (J. A. C. S., 1924, 1477; 1925, 260) that the change is ionic, and that the first stage is salt formation, e.g. chloride, acetate, benzoate, followed by rearrangement of the cation (for details cf. *Waters*, pp. 354–356). It is found, however, that the esters formed from an oxime and the chloride of a strong acid, e.g. benzenesulphonyl chloride, undergo transformation in the solid state without the need of a catalyst or the formation of ions:



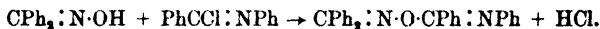
and the latter with mineral acid is hydrolysed to the amide  $R \cdot CO \cdot NHR$  and  $C_6H_5 \cdot SO_2OH$  (*Kuhara*, 1926). The efficiency of an acid chloride as a catalyst is directly proportional to the strength of the acid from which the chloride is derived, and the acetate ester can only undergo the *Beckmann* change in the presence of hydrochloric acid, i.e. a salt of the ester. The

picryl ethers behave in exactly the same way (J. C. S., 1933, 806; 1934, 1550; 1936, 448), and undergo spontaneous intramolecular rearrangement on heating.

The transformation by the aid of hydrochloric acid is not the simple formation of the chloride ester (Cl replacing OH) and its transformation, as the chloride  $\text{CR}_2\text{:NCl}$  does not undergo the *Beckmann* change. According to *Chapman* (*ibid.* 1935, 1223), who studied the change of benzophenone-oxime by HCl in ethylene dichloride solution, the change occurs in stages: (1) The slow formation of a small amount of benzanilide. (2) The reaction of this with HCl to give the imido chloride,



(3) Condensation of the oxime and imido chloride,



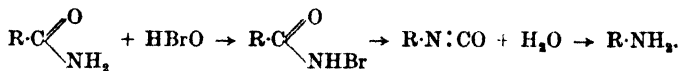
(4) The formation of the cation  $\text{CPh}_2\text{:N}\cdot\text{O}\cdot\text{CPh:NPh}^+$ .

This cation has the strongly electron-attracting group  $\cdot\text{CPh:NHPh}^+$  corresponding with the  $\text{C}_6\text{H}_5\cdot\text{SO}_2^+$  group.

It is highly probable that the rearrangement of esters may be due to powerfully acylous OX groups in compounds  $\text{R}_2\text{C:N}\cdot\text{OX}$  (esters of strong acids) or to the formation of an electron-attracting cation by salt formation or by both. The C ethers of oximes, which are not basic, do not undergo the *Beckmann* transformation.

## 2. The Hofmann Degradation.

This has already been referred to and consists in the conversion of an acid amide into an amine with one carbon atom less, the intermediate product being an isocyanate (p. 211):



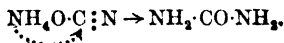
Analogous reactions are the conversion of a hydroxamic acid,  $\text{R}\cdot\text{CO}\cdot\text{NH}\cdot\text{OH}$ , by the loss of water into an isocyanate and then into an amine (*Lossen* reaction, 1877), and the de-

gradation of an acid azide  $\text{R}\cdot\text{C}\begin{array}{l} \nearrow \text{O} \\ \searrow \text{N}_2 \end{array}$  to an isocyanate, and hence

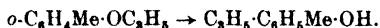
to an amine (*Curtius* degradation, 1901). All three reactions are characterized by the loss of carbon dioxide and the formation of an amine by the migration of an alkyl group from C to N. All three reactions take place in alkaline solution, and may be due to the action of OH on the CO group.

### D. Migration from O to C

1. **Urea Formation.**—The formation of urea by heating ammonium cyanate (Chap. XIII, C.) involves the breaking of an N-O bond and the formation of an N-C link:

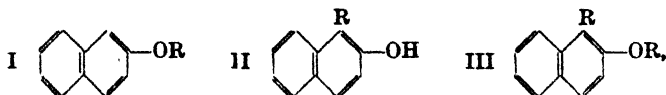


2. **Transformations of Allyl Ethers.**—Certain aryl allyl ethers when heated to 230° change over into *p*-allyl derivatives of phenols. One of the best-known examples is the conversion of guaiacol allyl ether into eugenol (2-hydroxy-5-allyl-toluene):



The allyl ether of phenol behaves in the same way, and by repeating the process, i.e. by converting the allyl phenol into its allyl ether and heating it is finally possible to obtain 2 : 4 : 6-triallylphenol.

The migration has been studied in the naphthalene series, where it has been found that  $\beta$ -naphthyl allyl ether I rearranges to 1-allyl-2-naphthol II, but 1-allyl-2-naphthyl allyl ether III does not suffer a migration of  $\text{C}_3\text{H}_5$  from  $\cdot\text{OC}_3\text{H}_5$  in position 2 to position 3:

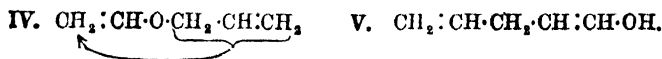


where R = allyl.

These facts have been used as an argument in favour of the symmetrical structure for naphthalene (Chap. XXXI), as in other cases the allyl group can only migrate to the adjacent carbon atom united by a double bond to the  $\text{:C} \cdot \text{OR}$  group;

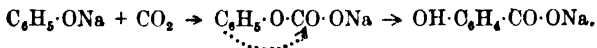


thus vinyl allyl ether IV at 250° yields allyl-acetaldehyde or enolic form:



(For discussion cf. *Baker and Lothian*, J. C. S., 1935, 628; also *Hurd and Pollack*, J. Org., 1939, 550.)

**3. Kolbe's Synthesis of Aromatic Hydroxy Acids.**—The conversion of the sodium derivatives of phenols into sodium salt of hydroxy-benzoic acids, with the formation of phenyl esters, e.g. sodium phenyl carbonate, as an intermediate product, is a well-known example of this type of migration:



The commonest examples is the synthesis of salicylic acid (Chap. XXVI, A3).

Other phenyl esters can undergo rearrangement in a similar manner.

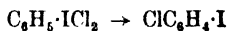
## E. Migration from O to N and N to N

The ethers of arylimines,  $\text{RO}\cdot\text{CR}:\text{NR}$ , where R represents aryl groups, at 220°, isomerize to diarylated acid amides,  $\text{O}:\text{CR}\cdot\text{NR}_2$ . Similarly amidines  $\text{R}\cdot\text{C}(\text{NRR}'):\text{NR}$  give  $\text{R}\cdot\text{C}(\text{NR}_2):\text{NR}'$ , i.e. an exchange between R and R' in the groups  $\cdot\text{NR}_2$  and  $:\text{NR}'$ . The second reaction is reversible, the former is not.

The reactions are unimolecular and intramolecular, as when two imino ethers are used the products are the two amides and not a mixed amide. The transformation is facilitated by the presence of electron-attracting substituents in the migrating radical.

### F. Migration from I to C

The gradual decomposition of phenyliodide-dichloride to a *p*-chloro-iodo-benzene is well known:



(Chap. XIX, B.). If the *p*-position is already occupied by OH, e.g. *p*-iodophol, the product is 2-chloro-4-iodophenol, probably formed from chlorine and *p*-iodophenol.

# HETEROCYCLIC COMPOUNDS

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## XXXIX. INTRODUCTION

This group includes the cyclic compounds which have a constituent atom other than carbon in the ring. The most common atom is nitrogen, and then oxygen and sulphur.

A few such compounds have been described in the earlier chapters, e.g. succinic anhydride, phthalimide, cyclic ethers, e.g. ethylene oxide, cyclic sugars, and purines.

The compounds are divided into groups according to the number of atoms constituting the ring, thus three-membered rings, e.g. ethylene oxide; four-membered rings, e.g. betaïne; five-membered rings, e.g. thiophene; six-membered rings, e.g. pyridine, &c. As in the carbocyclic series the most important and also the most stable are the five- and six-membered rings. A further division of these groups can be made according to the *number* of atoms other than carbon present. Thus in the five-membered ring compounds we can have the following sub-groups:  $4C + 1N$ ;  $3C + 2N$ ;  $2C + 3N$ ; termed respectively the monazole, di- and tri-azole sub-groups.

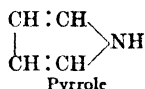
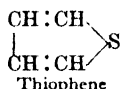
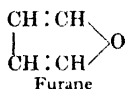
The stability of the compounds and their general chemical characteristics depend to a large extent on the saturated or unsaturated nature of the rings. Compounds like thiophene, pyrrole and pyridine are stable and closely resemble benzene—they possess general aromatic properties. Like benzene they can be reduced, the two former can each take up two or four atoms of hydrogen, and pyridine two, four or six. These reduction products no longer have aromatic properties. It is interesting to note that although the five-membered heterocyclic unsaturated compounds resemble benzene, the unsaturated carbocyclic compound cyclopentadiene does not.

Some of the common heterocyclic compounds contain condensed nuclei, i.e. the two condensed rings have two carbon

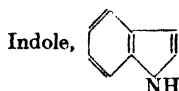
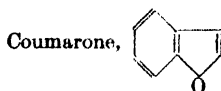
atoms in common. A well-known example of condensed heterocyclic rings is met with in purine and its derivatives (Chap. XIII, C.). Examples of compounds containing a benzene nucleus condensed with a heterocyclic ring are met with in quinoline, coumarone and indole (see below).

Compounds with condensed nuclei behave very differently on oxidation. Certain of them have the heterocyclic ring ruptured, and thus yield ortho-derivatives of the carbon ring; others, again, have the carbon ring ruptured, and yield ortho-acids of the heterocyclic ring. The compounds dealt with in the following sections will be grouped as follows:

1. Five-membered heterocyclic compounds containing 4C + 1O, S or N atoms, or the **furane** group, e.g.:

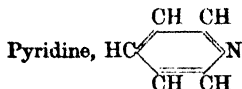


2. Compounds formed by the condensation of these rings with a benzene nucleus, e.g.:

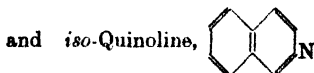
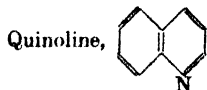


3. Five-membered heterocyclic compounds containing three carbon atoms, e.g. pyrazole and thiazole group.

4. Six-membered heterocyclic compounds or **pyridine** group, e.g.:



5. The compounds formed by the condensation of a benzene and pyridine ring, e.g.:



6. Six-membered heterocyclic compounds, with not more than four carbon atoms in the ring.

Compounds with P, As, Sb, Bi, Si, Pb, Hg, Fe, Te, Se, or I as constituents of the ring are also known. Most of these

compounds are formed from 1:5-dibromopentane,  $\text{BrCH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{Br}$ , or 1:4-dibromobutane and derivatives of the element in question. Thus sodium amalgam and the 1:5-

dibromo compound yield the product  $\text{CH}_2 \begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{Hg}$

(B., 1914, 177, 186; for Se and Te compounds cf. C. and I., 1939, 669). The *Grignard* compound derived from 1:5-dibromopentane reacts with  $\text{SiCl}_4$  or  $\text{SiMe}_2\text{Cl}_2$ , yielding the

products  $\text{CH}_2 \begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{SiCl}_2$  and  $\text{CH}_2 \begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{SiMe}_2$

(B., 1915, 1236), or, with  $\text{PbEt}_2\text{Cl}_2$ ,  $\text{CH}_2 \begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{PbEt}_2$

(B., 1916, 2666) as a colourless liquid, b.-pt.  $110^\circ/13.5$  mm. The same *Grignard* reagent reacts with phenylphosphine-

dichloride,  $\text{C}_6\text{H}_5\cdot\text{P}\cdot\text{Cl}_2$ , yielding  $\text{CH}_2 \begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{P}\cdot\text{C}_6\text{H}_5$

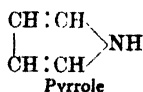
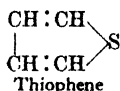
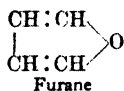
(B., 1915, 1473). When the *Grignard* compound from 1:4-dibromobutane is condensed with  $\text{CH}_3\cdot\text{P}\cdot\text{Cl}_2$ , compounds of the

type  $\begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{P}\cdot\text{CH}_3$  are formed, and derivatives containing

As, Sb, and Bi can be obtained by similar methods (B., 1916, 437).

These compounds are of no technical importance, but are of value from the theoretical point of view, and indicate the great variety of elements which can take part in ring formation.

## XL. FURANE GROUP



From these compounds a whole series of derivatives is obtained by the substitution of hydrogen by halogen, and also by the entrance of the groups  $\cdot\text{CH}_3$ ,  $\cdot\text{CH}_2\text{OH}$ ,  $\cdot\text{CHO}$ ,

$\cdot\text{CO}_2\text{H}$ , &c. In their properties furane, thiophene, and pyrrole resemble benzene. Thiophene, in particular, is delusively like the latter, e.g. in odour and boiling-point, and its various derivatives often show a marked similarity in their chemical and physical relations to the corresponding derivatives of benzene.

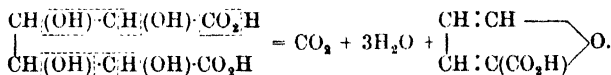
Furane, pyrrole, and thiophene also resemble one another in many respects. All three boil at relatively low temperatures ( $+32^\circ$ ,  $131^\circ$ ,  $84^\circ$ ), are either insoluble or only sparingly soluble in water, but readily in alcohol and ether, and show many analogous colour reactions. Thus pyrrole and thiophene and many of their derivatives give an intense violet to blue coloration when mixed with isatin and concentrated sulphuric acid, and a cherry-red or violet coloration with phenanthraquinone and glacial acetic or sulphuric acid. The vapour of pyrrole colours a pine shaving which has been moistened with hydrochloric acid carmine red ( $\pi\upsilon\pi\acute{\rho}\acute{\rho}\delta\varsigma$ , fiery-red), while furaldehyde vapour colours it an emerald green; the latter also colours a piece of paper moistened with xyloidine- or aniline-acetate red. Furane is converted by mineral acids, e.g. hydrochloric acid, into an insoluble amorphous powder, and pyrrole into an insoluble amorphous brown-red powder, "pyrrole-red" (with evolution of ammonia), while thiophene remains unaltered. Pyrrole has feebly basic properties.

Just as benzene is formed by the pyrogenic polymerization of acetylene (Chap. XVII, F), so several heterocyclic compounds are formed by the pyrogenic condensation of acetylene with  $\text{H}_2\text{S}$  or  $\text{NH}_3$  (*R. Meyer and Wechse*, B., 1917, 422). In the former case thiophene and thionaphthalene are formed; also thiotoluene if  $\text{CH}_4$  is also present. In the latter case the products include pyrrole, pyridine, quinoline, in addition to aniline, naphthalene, fluorene, and anthracene.

Maleic anhydride (Chap. X, B.) is regarded by *Pfeiffer* and *Botler* as the quinone of furane,  $\begin{array}{c} \text{CH}\cdot\text{CO} \\ \parallel \\ \text{CH}\cdot\text{CO} \end{array} \text{O}$ ; as such it yields coloured additive compounds with arylamines, phenols, phenolic ethers, and complex aromatic hydrocarbons (B., 1918, 1819).

Derivatives of all three compounds may be obtained from mucic acid,  $\text{CO}_2\text{H}\cdot(\text{CH}\cdot\text{OH})_4\cdot\text{CO}_2\text{H}$  (Chap. X, E.). When distilled, mucic acid yields pyromucic acid or furane- $\alpha$ -carboxylic

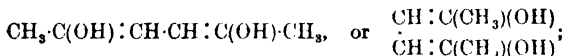
acid; when its ammonium salt is distilled, pyrrole is formed; and when free mucic acid is heated with barium sulphide, thiophene  $\alpha$ -carboxylic acid is obtained, e.g.:



Pyrrole derivatives are also formed by condensing  $\beta$ -ketonic esters (Chap. IX, H.) with amino-ketones (A., 1916, 411, 350).

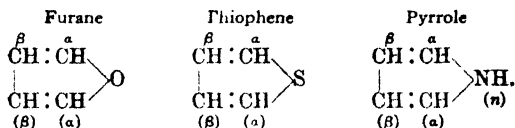
A very general method for the formation of derivatives of this group is from  $\gamma$ -diketones, e.g. acetyl-acetone,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_3$  (Chap. IX, F.). When this compound is heated with phosphorus pentoxide or zinc chloride, dimethyl-furane is formed; with phosphorus pentasulphide, dimethyl-thiophene; with alcoholic ammonia, dimethyl-pyrrole.

The acetyl-acetone reacts as the tautomeric enol:



and the formation of dimethyl-furane appears as that of an anhydride, that of dimethyl-pyrrole as an exchange of 2(OH) for NH (imide formation), and that of dimethyl-thiophene as the formation of a sulphide, i.e. exchange of 2(OH) for S.

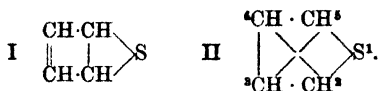
From the above reactions the *constitutional formulæ* for the three compounds would be:



These formulæ receive corroboration from the frequently observed fact that the substances are capable of yielding additive compounds with bromine or hydrogen (see Pyrroline). According to the above formulæ, two isomeric mono-substituted derivatives of furane and thiophene are possible: (1) one in which the hydrogen atom ( $\alpha$ ) which stands nearest to the oxygen, sulphur, or nitrogen atom, and (2) one in which a quasi-middle hydrogen atom ( $\beta$ ) is substituted. Two such isomers have been observed in many cases, e.g. two thiophenic acids. These form mixed crystals, the crystals having a homogeneous appearance although they contain both acids

(*V. Meyer*, A., **236**, 200). In the case of pyrrole, on the other hand, three kinds of derivatives ( $\alpha$ -,  $\beta$ -, and  $n$ -) are both possible and known.

An examination of the molecular refraction of thiophene and also of its heat of combustion (B., 1885, 1832) point to the presence of only one double bond in the thiophene molecule, and the formula I has been suggested, and also the centric formula II:



**Furane** or **furfurane** is a colourless mobile liquid, boiling at  $32^\circ$ , and with an odour resembling that of chloroform. It is present in pine-wood tar, in the first runnings from ordinary wood tar, &c., and is obtained by the distillation of sugar with lime, or by distilling barium pyromucate.  $\alpha$ -**Methyl-furane** or *sylvane* is likewise present in pine-wood tar, and in the products of distillation of sugar with lime. It boils at  $65^\circ$ .  $\alpha\alpha$ -**Dimethyl-furane** is obtained from sugar and lime, and also from acetonyl-acetone (p. 660). It is a colourless mobile liquid of a characteristic odour, and boils at  $94^\circ$ . Concentrated acids convert it into a resin; it can be transformed back into acetonyl-acetone.

**Fural**, *furfural*,  $\alpha$ -*furaldehyde* or *furfuraldehyde*,  $\text{C}_4\text{H}_3\text{O} \cdot \text{CHO}$  (*Döbereiner*), is obtained when pentoses, e.g. arabinose and xylose or the complex pentosans are distilled with concentrated hydrochloric acid:



The yield is quantitative, and the method is made use of for determining the amounts of pentoses present in various substances. It may also be obtained by distilling bran, corn-cobbs, wood, sugar, or various carbohydrates with moderately concentrated sulphuric acid, and is manufactured on a large scale in U.S.A. for use as a solvent, as a fungicide and disinfectant, also as a weed destroyer. It is also used for the manufacture of furoic acid and butyl furoate which are used in the lacquer industry. It is a colourless oil of agreeable odour, turns brown in the air, and boils at  $162^\circ$ .

It has the characteristic properties of an aldehyde, and can



yield condensation products in much the same manner as benzaldehyde (Chap. XXV, B.): viz. by the *Perkin* reaction it yields furyl- and allofuryl-acrylic acids,  $C_4H_3O \cdot CH:CH \cdot CO_2H$  (cf. Cinnamic Acid), by the benzoin condensation it yields furoin,  $C_4H_3O \cdot CH(OH) \cdot CO \cdot C_4H_3O$ , and by the *Knoevenagel* condensation ethyl furyl-malonate,  $C_4H_3O \cdot CH:C(CO_2Et)_2$ , and by the *Cannizzaro* reaction it yields equimolecular amounts of the alcohol and acid. With ammonia it yields a product, hydrofuramide, used in the synthetic resin industry.

**Pyromucic acid**,  $C_4H_3O \cdot CO_2H$ .—Furane- $\alpha$ -carboxylic acid crystallizes in needles or plates similar to those of benzoic acid, and melts at  $132^\circ$ ; it sublimes easily, is readily soluble in hot water and alcohol, and decolorizes alkaline permanganate almost instantaneously.

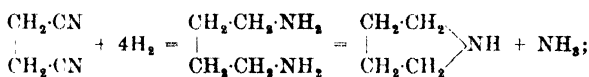
**Pyrrole** is a constituent of coal-tar (*Runge*) and of bone-oil (*Anderson*); it boils at  $131^\circ$ , and possesses, like many of its homologues, a chloroform odour. It is a secondary base, and its imino-hydrogen is replaceable by metals and alkyl, or acyl radicals.

In addition to the methods of formation mentioned on p. 660, it may also be obtained by heating succinimide (p. 274) with zinc dust, or from acetylene and ammonia at a red heat.

When pyrrole is acted upon by hydroxylamine the ring is broken, and the dioxime of succinic-aldehyde,  $\begin{matrix} CH_3 \cdot CH : N \cdot OH \\ CH_3 \cdot CH : N \cdot OH \end{matrix}$  is formed; this yields tetramethylene-diamine upon reduction. Dimethyl-pyrrole in a similar manner yields acetonyl-acetone-dioxime.

**n-Potassium-pyrrole**,  $C_4H_4NK$ , which is obtained from pyrrole and potassium or solid potassium hydroxide, is a colourless compound which is decomposed by water. A number of *n*-alkyl and acyl derivatives may be prepared by the aid of this potassium compound, but most of them are relatively unstable, and when heated are transformed into the isomeric  $\alpha$ -alkyl or acyl compounds. A most interesting reaction is the conversion of pyrrole into pyridine (Chap. XLIII, B.) by means of sodium methoxide and chloroform or methylene iodide. By the action of iodine and alkali, substitution takes place with the formation of **tetra-iodo-pyrrole** or **iodole**,  $C_4I_4(NH)$ , which crystallizes in yellow plates, and is used as an antiseptic in place of iodoform.

Zinc and glacial acetic acid convert pyrrole into **pyrroline**,  
 $\begin{array}{c} \text{CH:CH} \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{NH}$ , or more probably  $\begin{array}{c} \text{CH}\cdot\text{CH}_2 \\ || \\ \text{CH}\cdot\text{CH}_2 \end{array} \text{NH}$  (B., 1901, 3954), a colourless liquid boiling at 91° and also a strong secondary base; when this latter is heated with hydriodic acid, it is further reduced to **pyrrolidine**,  $\begin{array}{c} \text{CH}_2\cdot\text{CH}_2 \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array} \text{NH}$ , a colourless, strongly alkaline base resembling piperidine, and boiling at 86°. It is also formed by the action of sodium on an alcoholic solution of succinimide, and is obtained synthetically by heating  $\delta$ -chloro-butylamine with alkali, and by treating ethylene cyanide with sodium and alcohol, thus:



it is consequently designated **tetramethylene-imine** (*Ladenburg*).

Pyrrole forms complex condensation products with acetone and other ketones. These products probably contain 4 pyrrole nuclei attached to one another in the  $\alpha$ -positions by means of  $\text{CMe}_2$  groups.

Poly-alkyl-pyrroles are among the degradation products of hæmatin (the colouring matter of the blood) and of chlorophyll (the green colouring matter of plants) (Chap. LXIV, D.), and pyrrolidine-carboxylic acid (proline) is a degradation product of albumen.

**Thiophene** (*V. Meyer*, 1883) is present in coal-tar, being invariably found in benzene (up to 0.5 per cent); the same applies to its homologues thiotolene (methyl-thiophene), and thioxene (dimethyl-thiophene), which accompany toluene and xylene, &c. Its boiling-point (84°) is almost the same as that of benzene (80.4°), from which it is extracted by repeatedly shaking with small quantities of concentrated sulphuric acid, which transforms the thiophene into a soluble sulphonic acid. It is also attacked more readily than benzene by other reagents, such as halogens.

Thiophene is also obtained synthetically by leading the vapour of ethyl sulphide through a red-hot tube (*Kekulé*), in small quantity by heating crotonic acid, *n*-butyric acid, paraldehyde, with phosphorus pentasulphide, and in fairly large

quantities by passing acetylene over iron pyrites heated to  $300^{\circ}$  (*Steinkopf*, A., 1914, **403**, 1), or even better from a mixture of acetylene and  $\text{H}_2\text{S}$  over alumina at about  $400^{\circ}$ .

Stilbene (Chap. XXIX) and sulphur yield **tetraphenylthiophene**, *thionessal*, m.-pt.  $183^{\circ}$ .

The preparation and properties of the thiophene derivatives are almost identical with those of the corresponding benzene compounds. Thus nitric acid yields a **nitro-thiophene**, analogous to nitro-benzene, which can be reduced to amino-thiophene; the latter is, however, much less stable than the corresponding amino-benzene.

The boiling-points of thiophene compounds and their corresponding benzene derivatives are almost identical.

The homologues can be obtained by *Fittig's* synthesis, the  $\alpha$ -compounds from 1 : 4-diketones, and the  $\beta$ -derivatives from mono- or di-substituted succinic acids and phosphorus pentasulphide.

**Thiophene-sulphonic acid**,  $\text{OH}\cdot\text{SO}_2\cdot\text{C}_4\text{H}_3\text{S}$ , decomposes into thiophene and sulphuric acid when superheated with water, and does not yield a phenol on fusion with potash.

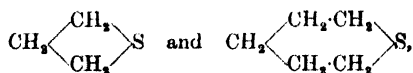
**Hydroxythiotolene**,  $\text{C}_4\text{H}_2\text{S}(\text{CH}_3)(\text{OH})$ , the phenol of thiotolene, is formed by heating lævulic acid with  $\text{P}_2\text{S}_5$ .

A mixture of the  $\alpha$ - and  $\beta$ -monocarboxylic acids when crystallized slowly from water yields **mixed crystals**, which cannot be resolved into their components.

The sulphur atom in thiophene is somewhat inert, but hydrogen peroxide converts tetraphenylthiophene into the **sulphone**  $\text{C}_4\text{Ph}_4\cdot\text{SO}_2$ .

**Tetrahydrothiophene** can be synthesized from 1 : 4-dibromobutane and sodium sulphide. It is a colourless liquid with an intense odour, boils at  $118^{\circ}$  and readily yields a sulphone.

The cyclic compounds,

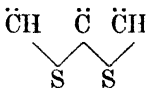


which are homologues of tetrahydrothiophene can be synthesized in a similar manner, and in properties closely resemble the alkyl sulphides,  $\text{R}_2\text{S}$  (Chap. IV, B.). The ring can be ruptured and unsaturated compounds obtained by first forming the sulphonium salt, e.g. addition of methyl iodide and subsequent treatment with alkali (*J. russ.*, 1916, **48**, 880-974), a reaction

analogous to the exhaustive methylation of nitrogen compounds (p. 689).

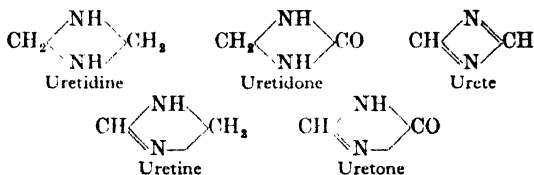
Ketones derived from thiophene are also known, e.g. 2-**acetyl-thiophene** from acetylchloride and thiophene-2-mercurichloride (A., 1914, **403**, 50).

A compound containing two condensed thiophene nuclei  $\text{CMe} \cdot \text{C} \cdot \text{CMe}$  is formed by heating *n*-octane and sulphur at high temperatures (Friedmann, B., 1916, 1344).



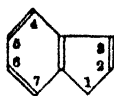
Four-membered rings containing two nitrogen or two sulphur atoms are known.

The following system of nomenclature has been suggested for the nitrogen compounds:



One of the simplest members is 1 : 4-**diphenyluretidone**, needles decomposing at 224° and formed by the action of a cold concentrated solution of potassium cyanate on benzylideneazine (p. 494) in glacial acetic acid (Hale, J. A. C. S., 1919, 370).

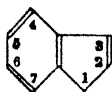
## XLI. COMPOUNDS FORMED BY THE CONDENSATION OF A BENZENE NUCLEUS WITH A FURANE, THIOPHENE, OR PYRROLE RING



Coumarone



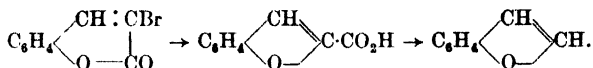
Benzo-thiophene



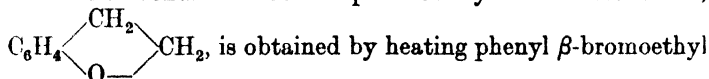
Indole

**A. Coumarone** occurs in coal-tar, and may be isolated as its **picrate**. It is usually obtained from bromocoumarin; this

with alcoholic potash yields coumarilic acid, which gives coumarone when distilled with lime:



It is a colourless liquid distilling at  $170^\circ$ ; yields a **dibromide** and a **dihydro**-derivative, thus indicating the presence of a double bond. A 30-40 per cent yield of **coumaran**,

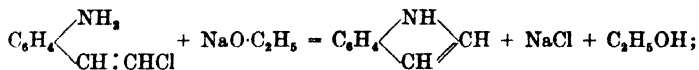


ether,  $\text{C}_6\text{H}_5 \cdot \text{O} \cdot \text{CH}_2 \cdot \text{CH}_2\text{Br}$ , from ethylene dibromide and sodium phenoxide, with  $\text{ZnCl}_2$  (J. A. C. S., 1919, 648).

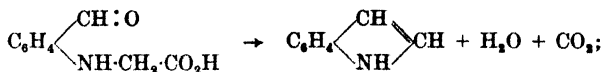
**Benzo-thiophene**, *Thionaphthene*, melts at  $31^\circ$ , boils at  $221^\circ$ , and has an odour resembling naphthalene.

## B. Indole Group

**Indole** (*Baeyer*, 1868) is important as it is the parent substance of indigo. As a pyrrole derivative it has feebly basic properties. It is obtained by distilling oxindole with zinc dust; by heating *o*-nitro-cinnamic acid with potash and iron filings; by the action of sodium ethoxide upon *o*-amino- $\beta$ -chloro-styrene (B., 1884, 1067):



by the elimination of water and carbon dioxide from *o*-aldehyde-phenylglycine under the influence of acetic anhydride:



or by the pancreatic fermentation of albumen; together with skatole by fusing albumen with potash; and by passing the vapours of various anilines, e.g. diethyl-*o*-toluidine, through red-hot tubes, &c. It occurs in the essential oil of jasmine flowers, crystallizes in plates, melts at  $52^\circ$ , volatilizes readily with steam, and usually has a peculiar faecal-like odour, although in the pure state and diluted it is stated to have a fragrant odour. It colours a pine shaving which has been

moistened with hydrochloric acid cherry-red, with nitrous acid gives a red precipitate, which consists partly of the so-called nitroso-indole,  $[C_8H_6N(NO)]_2$  (a delicate reaction; see B., 1889, 1976), and yields acetyl-indole when acetylated. These last reactions show that indole contains an imino-group. When oxidized with ozone it yields indigo.

The system of numbering the substituents in the indole molecule is given on p. 665. The 1-substituted derivatives are sometimes termed *n*-derivatives, e.g. *n*-methyl-indole,



Various derivatives may be obtained synthetically by the condensation of the aromatic primary or secondary hydrazines either with pyroracemic acid or with certain ketones or aldehydes, and treatment of the resulting hydrazones with dilute hydrochloric acid or zinc chloride, when ammonia is eliminated (*E. Fischer*); thus acetone-phenyl-hydrazone,  $C_6H_5 \cdot NH \cdot$

$N:C \begin{array}{l} \swarrow CH_3 \\ \searrow CH_3 \end{array}$ , yields 2-methyl-indole,  $C_6H_4 \begin{array}{l} \swarrow NH \\ \searrow CH \end{array} \begin{array}{l} \nearrow C \cdot CH_3 \\ \searrow \end{array}$ , prop-aldehyde-phenyl-hydrazone yields skatole, and phenacyl bromide and aniline yield 2-phenyl-indole.

**Skatole, 3-methyl-indole**,  $C_6H_4 \begin{array}{l} \swarrow NH \\ \searrow CMe \end{array} \begin{array}{l} \nearrow CH \\ \searrow \end{array}$ , is found in fæces,

and is produced, together with indole, e.g. by the decay of albumen, or by fusing it with potash. It crystallizes in colourless plates, m.-pt. 95°, and when impure has a strong fæcal odour. The pure compound obtained by the hydrolysis of beet-sugar molasses has a fruity odour and is used as strawberry flavour. Nitrous acid does not colour it red. It takes up two atoms of hydrogen to form a hydro-compound. Acids, aldehydes, &c., are also known.

**Dioxindole**,  $C_6H_4 \begin{array}{l} \swarrow CH(OH) \\ \searrow NH \end{array} \begin{array}{l} \nearrow CO \\ \searrow \end{array}$ , or the lactam of *o*-amino

mandelic acid,  $NH_2 \cdot C_6H_4 \cdot CH(OH) \cdot CO_2H$ , is obtained by the reduction of isatin with zinc dust and hydrochloric acid, or by the oxidation of oxindole. It crystallizes in colourless prisms, melts at 180°, and possesses both basic and acid properties (two hydrogen atoms being replaceable); it also

forms a nitroso-compound, an N-acetyl derivative, and is readily oxidized to isatin.

**Oxindole**,  $C_6H_4 \begin{array}{c} \text{NH} \\ \diagdown \quad \diagup \\ \text{CH}_2 \end{array} \text{CO}$ , the lactam of *o*-amino-phenyl-

acetic acid, is formed by the reduction of *o*-nitro-phenyl-acetic acid (p. 520); also by that of dioxindole with tin and hydrochloric acid. It crystallizes in colourless needles, melts at  $120^\circ$ , is readily oxidized to dioxindole, and therefore possesses feebly reducing properties. Oxindole is amphoteric, dissolving both in alkalis and in hydrochloric acid. Baryta water at a somewhat high temperature transforms it into barium *o*-amino-phenyl-acetate. The imino-hydrogen is exchangeable for ethyl, acetyl, the nitroso-group, &c.

Isomeric with oxindole is **indoxyl**,  $C_6H_4 \begin{array}{c} \text{NH} \\ \diagdown \quad \diagup \\ \text{C(OH)} \end{array} \text{CH}$ , which

is obtained by the elimination of carbon dioxide from indoxylic acid, a product formed from phenyl-glycocol (p. 520), also by fusing indigo with potash. It is often present in the urine of the carnivora as potassium indoxyl-sulphate or urine-indican,  $C_8H_6N \cdot O \cdot (SO_3K)$ . It forms yellow crystals, melting at  $85^\circ$ , is moderately soluble in water with yellow fluorescence, and not volatile with steam. It is very unstable, quickly becoming resinous, and is readily transformed into indigo when its alkaline solution is exposed to the air, or when ferric chloride is added to its solution in hydrochloric acid.

It yields a nitroso-compound,  $C_6H_4 \begin{array}{c} \text{N(NO)} \\ \diagdown \quad \diagup \\ \text{C(OH)} \end{array} \text{CH}$ , of the same character as the nitrosamines, and therefore it contains an imino-group; further, its relation to indoxyl-sulphuric acid shows that it contains an alcoholic hydroxy-group, and thus its constitution follows.

**Potassium indoxyl-sulphate**, prepared synthetically by warming indoxyl with potassium pyrosulphate, crystallizes in glistening plates and is hydrolysed when warmed with acids.

**Ethyl-indoxyl** is obtained from indoxyl by the exchange of the hydroxylic hydrogen for  $C_2H_5$ . Derivatives of the hypo-

thetical **pseudo-indoxyl**,  $C_6H_4 \begin{array}{c} \text{NH} \\ \diagdown \quad \diagup \\ \text{CO} \end{array} \text{CH}_2$ , are also known,

some of them being convertible into indigo derivatives (e.g. diethyl-indigo).

**Indoxylic acid**,  $C_6H_4 \begin{smallmatrix} \diagup NH \diagdown \\ \diagdown C(OH) \diagup \end{smallmatrix} C \cdot CO_2H$ , the 2-carboxylic

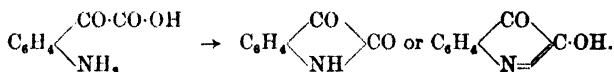
acid of indoxyl, forms white crystals, is oxidized to indigo by ferric chloride, and breaks up into indoxyl and carbon dioxide when fused. It is obtained from its ester, **ethyl indoxylate**, by heating with soda. The latter compound crystallizes in stout prisms, melts at  $120^\circ$ , and may be obtained, among other methods, by the reduction of ethyl *o*-nitro-phenyl-propiolate with ammonium sulphide.

**Isatin**,  $C_6H_4 \begin{smallmatrix} \diagup CO \diagdown \\ \diagdown NH \diagup \end{smallmatrix} CO$ , the lactam of *o*-amino benzoyl-

formic acid (p. 531), is readily prepared by oxidizing indigo or indoxyl with nitric acid (*Erdmann* and *Laurent*, 1841; cf. also B., 1884, 976). It may also be obtained by the oxidation of dioxindole or of oxindole (indirectly).

The following are among some of the most important methods by means of which isatin has been synthesized:

(a) When *o*-nitro-phenyl-glyoxylic acid (*o*-nitro-benzoyl-formic acid, p. 531) is reduced, the corresponding amino-acid is obtained; but this immediately loses water, yielding a lactam or lactim:



(b) *o*-Nitro-phenylacetic acid when reduced yields the lactam, oxindole,  $C_6H_4 \begin{smallmatrix} \diagup CH_2 \diagdown \\ \diagdown NH \diagup \end{smallmatrix} CO$ , and this with nitrous acid gives the iso-nitroso-oxindole,  $C_6H_4 \begin{smallmatrix} \diagup C(:N \cdot OH) \diagdown \\ \diagdown NH \diagup \end{smallmatrix} CO$ , which

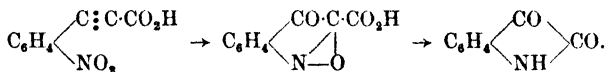
on reduction is converted into amino-oxindole, and this on oxidation with ferric chloride yields isatin.

(c) *Sandmeyer* has worked out the following synthesis: Aniline and carbon disulphide readily yield thio-carbanilide,  $CS(NHC_6H_5)_2$ , which, on boiling with potassium cyanide, white-lead, and water, yields hydrocyano-carbo-diphenyl-imide,  $C_6H_5 \cdot N : C(CN) \cdot NHC_6H_5$ . With ammonium sulphide

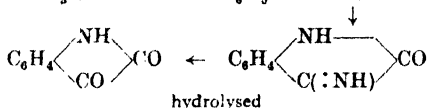
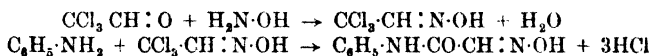


this latter yields  $\text{NH}_2\cdot\text{CS} \begin{array}{c} \diagup \\ \text{C} \end{array} \begin{array}{c} \diagdown \\ \text{N} \end{array} \text{C}_6\text{H}_5$ , which is converted by concentrated sulphuric acid into  $\alpha$ -isatin-anilide,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CO} \\ \diagdown \text{N} \end{array} \text{C} \begin{array}{c} \diagup \\ \text{C} \end{array} \begin{array}{c} \diagdown \\ \text{N} \end{array} \text{C}_6\text{H}_5$ , and this may be hydrolysed by dilute acids to isatin and aniline (C. C., 1900, 2, 928).

(d) *o*-Nitrophenyl-propionic acid (p. 524) may be synthesized, and when this is warmed with alkalis it undergoes molecular rearrangement and yields **isatogenic acid**, which by elimination of carbon dioxide forms isatin:



(e) Isatin and its homologues are readily formed by condensing aniline or substituted anilines with a freshly prepared solution of hydroxylamine sulphate and chloral hydrate (*Sandmeyer*, *Helv.*, 1919, 234).



or (f) By internal condensation of substituted oxamic chlorides, e.g.  $\text{C}_6\text{H}_5\text{NR}\cdot\text{CO}\cdot\text{CO}\cdot\text{Cl}$  with  $\text{AlCl}_3$  (*Stollé*, *B.*, 1913, 3915; *J. pr.*, 1922, [2], 105, 137).

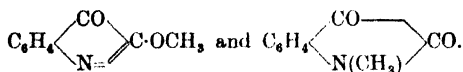
Isatin crystallizes in reddish-yellow prisms, sparingly soluble in cold water, but more readily in hot water or alcohol. It dissolves in potassium hydroxide solution, yielding the potassium

derivative,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CO} \\ \diagdown \text{N} \end{array} \text{C}=\text{OK}$ , which is readily hydrolysed to potassium *o*-amino-phenyl-glyoxylate when boiled with water.

**Isatin chloride**,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CO} \\ \diagdown \text{N} \end{array} \text{C}=\text{Cl}$ , is obtained when isatin is

heated with phosphorus pentachloride, and on reduction with zinc dust and acetic acid yields indigo.

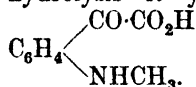
Two isomeric methyl ethers are known:



O-methyl-isatin      N-methyl-isatin or pseudo-methyl-isatin

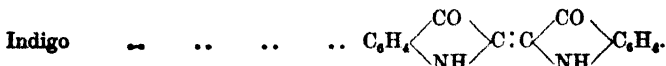
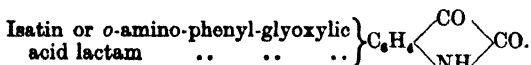
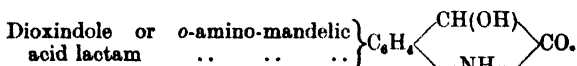
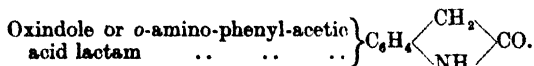
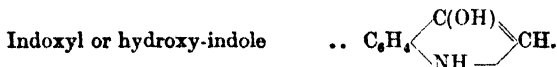
The O-ether is obtained by converting potassium-isatin into the silver compound, and then heating this with methyl iodide. It is a colourless solid melting at  $102^\circ$ , and on hydrolysis yields isatin or *o*-amino-phenyl-glyoxylic acid.

The N-ether may be obtained by the action of sodium hypobromite on N-methyl-indole. Its constitution follows from its method of formation, and also from the fact that on hydrolysis it yields *o*-methyamino-phenyl-glyoxylic acid,



The constitution of isatin itself for some years was a matter of dispute; from its method of formation it must be either the lactam or lactim of *o*-amino-phenyl-glyoxylic acid. The examination of its absorption spectrum has established its lactam structure (Chap. LXXI, D.).

### C. Indigo and Related Compounds



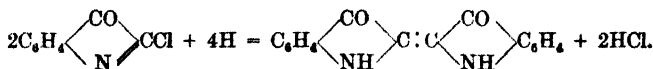
**Indigo**, which is obtained from the indigo plant (*Indigofera tinctoria*), and from woad (*Isatis tinctoria*), has been known for thousands of years as a valuable blue dye, especially for woollen fabrics. In addition to indigo-blue (indigotin), commercial indigo contains indigo-gelatine, indigo-brown, and indigo-red, all of which can be extracted from it by solvents. The colouring matter is not present as such in the indigo plant, but as the glucoside of indoxyl "**Indican**", from which it can be prepared either by dilute acids or certain enzymes and subsequent oxidation with atmospheric oxygen.

It forms a dark-blue coppery and shimmering powder or, after sublimation, copper-red prisms, insoluble in most solvents (including the alkalis and dilute acids), but dissolving to a blue solution in hot aniline and to a red one in paraffin, from either of which it may be crystallized. Its vapour is dark-red. The formula  $C_{16}H_{10}O_2N_2$  is confirmed by its vapour density. It is converted by reducing agents, such as ferrous sulphate and caustic soda solution or grape-sugar and soda, into the leuco-compound, **indigo-white**,  $C_{16}H_{12}O_2N_2$ , a white crystalline powder soluble in alcohol and ether, also in alkalis (as a phenol); the alkaline solution quickly becomes oxidized by the oxygen of the air, with the separation of a blue film of indigo. It yields an acetyl compound which crystallizes in colourless needles.

Warm concentrated or fuming sulphuric acid dissolves indigo to **indigo-monosulphonic** and **disulphonic acids**, the former of which (termed phœnicin-sulphonic acid) is sparingly soluble in water, but the latter readily so; the sodium disulphonate is the **indigo-carmin** of commerce. Nitric acid oxidizes indigo to isatin, while distillation with potash yields aniline, and heating with manganese dioxide and a solution of potash, anthranilic acid.

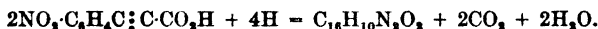
Indigo has been prepared synthetically by numerous methods. The following are among the most important:

1. By the reduction of isatin chloride (p. 670) with zinc dust and acetic acid:

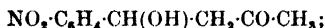


The syntheses of isatin already described (pp. 669 and 670) are thus syntheses of indigo.

2. By warming *o*-nitro-phenyl-propionic acid with grape-sugar in alkaline solution (*Baeyer*, 1880):



3. *Baeyer* and *Drewson* (1882) started with toluene, and on nitration obtained a mixture of *o*- and *p*-nitro-toluenes. The *o*-compound was oxidized by manganese dioxide and sulphuric acid to *o*-nitro-benzaldehyde, and this was then condensed with acetone, yielding *o*-nitro-phenyl-lactyl methyl ketone,

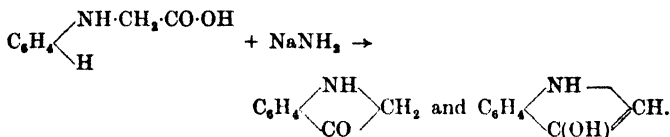


which when warmed with alkalis gave indigo and water. The yield was good, but the method was of no great practical importance, as the amount of toluene is limited, and no use could be found for the *p*-nitro-toluene obtained as a by-product.

4. In 1890 *Heumann* obtained **phenyl-glycocoll**, *phenyl-glycine*, by the condensation of aniline with chloracetic acid:



and when this was fused with alkali, indigo-white was obtained. Another method is to treat the phenylglycine with sodamide and to oxidize the product, indoxyl, to indigo:

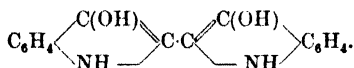


A modified form of *Heumann's* synthesis consists in condensing anthranilic acid (p. 519) with chloracetic acid, when phenylglycine-*o*-carboxylic acid is obtained, and this on fusion with alkali yields indoxyl, which oxidizes in the air to indigo-blue. The yield is good, and this method is now employed on a manufacturing scale by the "Badische Anilin Fabrik" for the production of artificial indigo, as anthranilic acid can be obtained cheaply; the general method being the atmospheric oxidation of naphthalene with a suitable catalyst to phthalic anhydride (Chap. XXVI, B.), and the conversion of this into phthalimide by the aid of ammonia. The phthali-

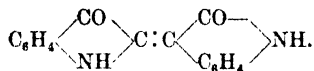
amide with alkali and chlorine yields anthranilic acid—*o*-amino-benzoic acid (*Hofmann* reaction, p. 211).

For homologues and derivatives cf. Chap. LIX, K1.

Indigo-blue is a very valuable blue dye, on account of its "fastness" to light, alkalis, acids, and soaps. As indigo-blue itself is insoluble, its "leuco" compound indigo-white is usually employed, the fabric being immersed in an alkaline solution of this, and then exposed to the air, when oxidation to indigo-blue takes place. Indigo-blue is usually reduced to indigo-white by means of calcium hyposulphite or by glucose and caustic soda. The indigo-white is a colourless solid with phenolic properties, and probably has the constitution represented in the formula:



**Indirubin**, *Indigo-purpurin*, is an isomeride of indigo-blue, and can be obtained synthetically by the condensation of isatin and indoxyl in alkaline alcoholic solution:



It is also obtained, together with indigo-blue, by the reduction of isatin chloride. It crystallizes from aniline in chocolate-brown needles, and on oxidation yields isatin.

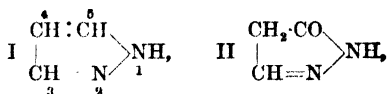
(For history and manufacture of indigo see J. S. C. I., 1901, 239, 332, 551, 802; J. C. S., 1905, 974.)

## XLII. PYRAZOLE GROUP, ETC.

### A. Pyrazole Group\*

This comprises compounds with a five-membered ring containing three carbon and two nitrogen, sulphur, or oxygen atoms.

\* For review of pentacyclic nitrogen compounds containing 1 to 4 N atoms compare *Chem. Rev.*, 1935, 305. In all such compounds containing —C—N—N—C=N— links the dipole is of the type C positive and N negative end.

**Pyrazole (I),**

is theoretically derivable from pyrrole in the same way as pyridine is from benzene, i.e. by the exchange of CH for N.

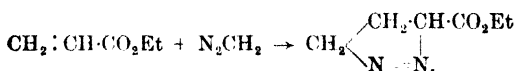
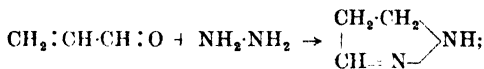
The positions three and five appear to be identical unless the H of the NH is replaced by alkyl groups.

It is a weak base of great stability, crystallizing in colourless needles; it melts at  $70^\circ$ , boils at  $185^\circ$ , and possesses aromatic properties (B., 1895, 714). Its simplest synthesis is by the union of acetylene and diazo-methane:



(Von Pechmann, B., 1897, 2950; see also B., 1890, 1103; A., 273, 214).

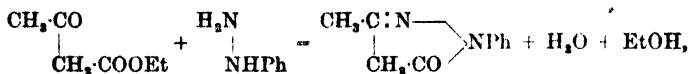
**Pyrazoline**,  $\text{C}_3\text{H}_6\text{N}_2$ , and **pyrazolidine**,  $\text{C}_3\text{H}_8\text{N}_2$ , are reduction products of pyrazole. Pyrazoline derivatives can be synthesized by condensing hydrazines with  $\alpha$ -olefinic aldehydes or ketones (B., 1918, 1457), or aliphatic diazo compounds with unsaturated esters (A., 1929, 470, 284).



Characteristic of many of these pyrazoline derivatives is the readiness with which they give up nitrogen when heated and yield corresponding derivatives of trimethylene (Kishner, Abs., 1912, i, 245; 1913, i, 1163; 1916, i, 290).

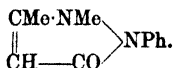
**Pyrazolone (II)** is an oil boiling at  $77^\circ$ .

**1-Phenyl-3-methyl-pyrazolone**, obtained by the action of phenylhydrazine on ethyl acetoacetate (p. 263),



crystallizes in compact prisms, melts at  $127^{\circ}$ , and boils without decomposition. As a weak base it dissolves in acids, but is also soluble in alkalis; it further contains the chemically-active methylene group. When methylated it yields:

1-Phenyl-2 : 3-dimethyl-pyrazolone or **antipyrine**,  $C_{11}H_{12}N_2O$ , which is also formed by the action of ethyl acetoacetate upon methyl-phenyl-hydrazine, and therefore possesses the constitutional formula (*L. Knorr, A., 238, 137*),

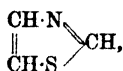


It crystallizes in small colourless plates melting at  $113^{\circ}$ . The aqueous solution is coloured red by ferric chloride and blue-green by nitrous acid. Antipyrine is an excellent febrifuge.  $\beta$ -Ketonic acids,  $\beta$ -ketonic aldehydes,  $\beta$ -diketones also yield pyrazole derivatives with phenyl-hydrazine.

Isomeric with pyrazole is glyoxaline (p. 677), in which the two atoms of N are separated by a C atom.

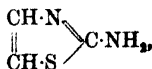
## B. Thiazole Group

### Thiazole,

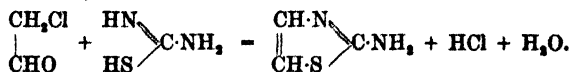


is derived from thiophene in the same way as pyridine is from benzene, by the exchange of CH for N, and closely resembles—along with its derivatives—the bases of the pyridine series in properties. It is obtained from amino-thiazole (see below) by the exchange of the amino-group for hydrogen, in a similar manner to the conversion of aniline into benzene. It is a colourless liquid, boiling at  $117^{\circ}$ , hardly distinguishable from pyridine; as a base it forms salts, but it is scarcely affected by concentrated sulphuric acid, &c. (*Hantzsch, Popp, A., 250, 273*).

### Amino-thiazole,

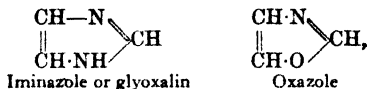


is formed by the action of mono-chloraldehyde upon thio-urea (pseudo form):

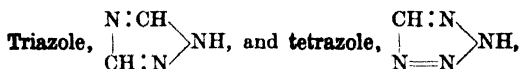


The constitution of the thiazoles follows from this and similar modes of formation. Amino-thiazole is a base with aromatic properties closely resembling aniline and can be diazotized (cf. *Hantzsch* and his pupils, A., 249, 1, 7, 31; 250, 257; 265, 108).

As further types of five-membered rings, may be cited:



which are related to thiazole as pyrrole and furane are to thiophene. An important derivative of iminazole is Histidine (cf. *Proteins*, Chap. LXVII).



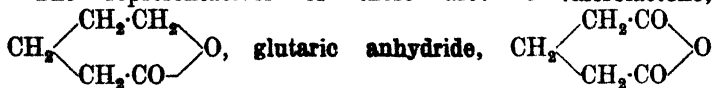
are examples of five-membered rings extremely rich in nitrogen.

The foregoing constitutional formulæ with their double linkings correspond with *Kekulé's* benzene formula. But formulæ with centric linkings analogous to the centric benzene formula (p. 392) have been introduced. According to *Robinson*, the six aromatic electrons of benzene can be represented in these compounds by the 4 carbon electrons and the pair of lone electrons of the O, S or N atom.

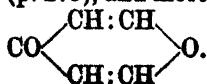
### XLIII. SIX-MEMBERED HETEROCYCLIC RINGS

Ring compounds closely related to pyrrole, thiophene, and furane, but containing six atoms in the ring (viz. five carbon atoms + one oxygen, sulphur, or nitrogen atom), are known.

The representatives of these are:  $\delta$ -valerolactone,



(p. 275), and more especially the pyrones, e.g. 1:4- or  $\gamma$ -pyrone,





The parent substances of the pyrones are the pyrans, viz

1:2- or  $\alpha$ -pyran,  $\text{O} \begin{array}{c} \text{CH}_2\text{CH} \\ \text{CH:CH} \end{array} \text{CH}$ , and 1:4- or  $\gamma$ -pyran,  $\text{O} \begin{array}{c} \text{CH:CH} \\ \text{CH:CH} \end{array} \text{CH}_2$ . Corresponding with the 1:2-pyran is the 1:2-pyrone,  $\text{O} \begin{array}{c} \text{CO-CH} \\ \text{CH:CH} \end{array} \text{CH}$ , which is the lactone of 5-hydroxy-penta- $\Delta^{2,4}$ -diene-1-acid.

Of the nitrogen compounds, **pyridine**,  $\text{CH} \begin{array}{c} \text{CH-CH} \\ \text{CH:CH} \end{array} \text{N}$ , and **piperidine**,  $\text{CH}_2 \begin{array}{c} \text{CH}_2\text{-CH}_2 \\ \text{CH}_2\text{-CH}_2 \end{array} \text{NH}$ , are of great importance.

The derivatives of the sulphur compound, **penthiofene**,  $\text{CH}_2 \begin{array}{c} \text{CH:CH} \\ \text{CH:CH} \end{array} \text{S}$ , are of but little importance.

Six-membered rings containing two nitrogen atoms are the diazines,  $\text{C}_4\text{H}_4\text{N}_2$ , the ortho compound is *pyridazine*, the meta *pyrimidine*, and the para *pyrazine*. The compound,

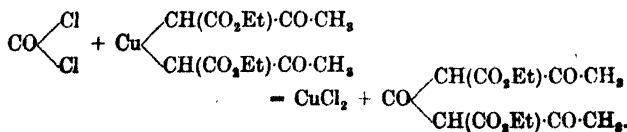
$\text{NH} \begin{array}{c} \text{CH}_2\text{-CH}_2 \\ \text{CH}_2\text{-CH}_2 \end{array} \text{O}$ , is *morpholin*. Six-membered rings containing three and four nitrogen atoms are termed respectively triazines and tetrazines (cf. Triazole and Tetrazole, p. 677).

### A. Pyrones

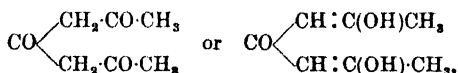
**1:4-Pyrone**, a solid, m.-pt.  $32.5^\circ$  and b.-pt.  $315^\circ$ , is obtained when its dicarboxylic acid, chelidonic acid (p. 680), is

heated. **2:6-dimethyl-1:4-pyrone**,  $\text{CO} \begin{array}{c} \text{CH:CMe} \\ \text{CH:CMe} \end{array} \text{O}$ , may

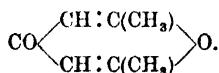
be synthesized from cupric ethyl aceto-acetate and carbonyl chloride.



On hydrolysis with sulphuric acid the ester yields the free acid, which loses carbon dioxide, yielding:



which immediately loses water, yielding dimethyl- $\gamma$ -pyrone:



(For a modified formula see *Collie*, J. C. S., 1904, 971.) *Collie* and *Tickle* (J. C. S., 1899, 710) have shown that this compound can form definite salts with acids, e.g. the hydrochloride,  $\text{C}_7\text{H}_8\text{O}_2$ , HCl, and oxalate. The addition of the acid undoubtedly occurs at the oxygen atom, and not by the addition of HCl to a double bond, since the salts are relatively unstable and are completely hydrolysed in dilute aqueous solution. The oxygen atom in these salts, therefore, probably functionates

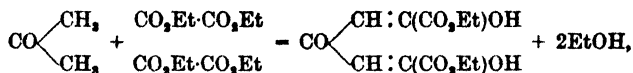
as a quadrivalent atom,  $\begin{array}{c} \cdot\text{C} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{O} \\ \diagup \quad \diagdown \\ \cdot\text{C} \quad \text{Cl} \end{array}$ , or  $\begin{array}{c} \cdot\text{C} \\ \diagdown \\ \text{O}^+ \rightarrow \text{H} \text{ and } \bar{\text{Cl}}, \text{ and} \\ \diagup \\ \cdot\text{C} \end{array}$

the salts are **oxonium salts** corresponding with **ammonium salts**. Numerous other compounds have since been obtained, which tend to show that the oxygen atom can frequently functionate in this manner, e.g. numerous oxygen compounds, esters, ethers, ketones, acids, aldehydes yield definite crystalline compounds with anhydrous metallic salts, e.g.  $\text{MgBr}_2$  or  $\text{AlCl}_3$  (*Walker*, J. C. S., 1904, 1106); similar oxygen compounds also form well-defined crystalline salts with complex acids, e.g. ferrocyanic acid (*Baeyer* and *Villiger*, B., 1901, 2679, 3612; 1902, 1201); and even mineral acids (for summary of work see *Knox* and *Richards*, J. C. S., 1919, 508). Since the salt is derived from a very feeble base (solutions of dimethyl-pyrone are very feeble conductors) and a relatively strong acid, the solution should be highly hydrolysed, and should give a strongly acid reaction. That the hydrolysis is not complete in the case of a moderately concentrated solution of the picrate has been shown by *Walden* (B., 1901, 4191), who compared the partition coefficient of picric acid between water and benzene both with and without the addition of dimethyl-pyrone,

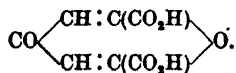
and found that the ratio  $\frac{\text{concentration of benzene solution}}{\text{concentration of aqueous solution}}$  is less when the pyrone is present.

Other methods which have also led to the conclusion that a certain amount of salt exists in solution are (a) depression of the freezing-point of aqueous solutions. If no compound exists in an aqueous hydrochloric acid solution, then the depression caused would be the sum of the depressions produced by the known amounts of dimethyl-pyrone and hydrochloric acid present. The actual value obtained is less than this sum (*Walden*). (b) A determination of the electrical conductivity. If no compound is formed, the conductivity should be the same as that of a solution of pure hydrochloric acid of the same concentration; but if any appreciable amount of a salt is formed in solution this will give rise to a certain number of pyrylium (+) and chloride (-) ions, i.e. the number of hydrions will be less than in a solution of pure hydrochloric acid of the same concentration, and hence the electrical conductivity will be considerably reduced. It has actually been found that the conductivity is less, and that it tends to decrease as the solution becomes more concentrated (cf. also *Rordam*, J. A. C. S., 1915, 557).

**$\gamma$ -Pyrone-dicarboxylic acid**, or chelidonic acid, occurs in the greater celandine (*Chelidonium majus*), and may be synthesized by *Claisen's* method (p. 257). Acetone and ethyl oxalate readily condense, yielding the ester of acetone-dioxalic acid or xantho-chelidonic acid:



which immediately loses water, yielding ethyl chelidonate, and this on careful hydrolysis yields chelidonic acid:



The salts of this acid are colourless, but when warmed with an excess of alkali yellow salts of xantho-chelidonic acid are formed owing to the rupture of the ring.

Pyrone with hydrogen in the presence of palladium and gum-arabic yield tetrahydro-derivatives, which boil at lower

temperatures than the original substances. Pyrones in colloidal solution or as gels adsorb iodine, giving blue products, more especially 8-phenyl- $\gamma$ -benzopyrone (*Barger and Starling*, J.C.S., 1915, 411; *A. R. Watson*, 1916, 303).

## B. Pyridine

**Pyridine**,  $C_5H_5N$ , resembles benzene in many points:

1. It is even more stable than benzene, and yields substituted derivatives with sulphuric and nitric acids or the halogens, but not so readily as benzene. Sulphonic acids are obtained at very high temperatures only, and only a few chloro- and bromo-pyridines have been prepared. Pyridine and its carboxylic acids are not affected by oxidizing agents.

2. Its derivatives resemble those of benzene. Thus its homologues (and also quinoline, &c.) are transformed into pyridine-carboxylic acids when oxidized, and these acids yield pyridine when distilled with lime, just as benzoic acid yields benzene.

3. The isomeric relations are also precisely analogous to those of the benzene derivatives. Thus the number of the isomeric mono-derivatives of pyridine is the same as that of the isomeric bi-derivatives of benzene, viz. three; and the number of the bi-derivatives of pyridine, containing the same substituents, the same as that of the benzene derivatives,  $C_6H_3X_3$ , viz. six.

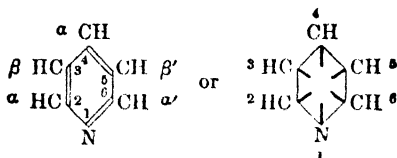
4. Just as two benzene nuclei can form naphthalene, so can a benzene and a pyridine form the compound quinoline:



5. The products of reduction are likewise analogous. Pyridine like benzene yields a hexahydro-derivative,  $C_5H_{11}N$ , only somewhat more readily; this is known as piperidine. Quinoline yields a tetrahydro-derivative,  $C_9H_{11}N$ , more readily than naphthalene, and acridine readily yields a dihydro-derivative,  $C_{13}H_{11}N$ , which is analogous to anthracene dihydride. In these latter compounds further combination with hydrogen may take place, but there is likewise a tendency to the reproduction of the original bases.

Hence the conclusion is drawn that pyridine has a ring

constitution similar to that of benzene, and is to be represented as:



In contradistinction to the neutral benzene hydrocarbons, pyridine and its homologues are bases of the same order of strength as aniline and have characteristic odours. Pyridine is readily soluble in water, but quinoline only slightly so. They distil or sublime without decomposition, and form salts; those with hydrochloric and sulphuric acids are for the most part readily soluble, while those with chromic acid or hydroferrocyanic acid, though often characteristic, are usually only sparingly soluble; they also form double salts with the chlorides of platinum, gold and mercury, most of which are sparingly soluble, e.g.  $(\text{C}_5\text{H}_5\text{N})_2\text{H}_2\text{PtCl}_6$ .

The bases are tertiary, and hence cannot be acetylated; they combine, however, with alkyl iodides, yielding quaternary ammonium salts, e.g. pyridine and methyl iodide yield  $\text{C}_5\text{H}_5\text{N}$ ,  $\text{CH}_3\text{I}$ , **methyl-pyridonium iodide**.

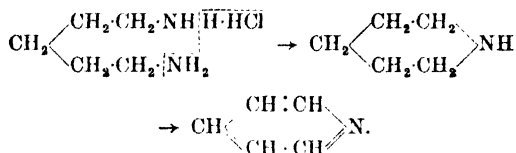
Pyridine and some of its homologues are present in coal-tar, and are therefore constituents of the lower boiling fractions. They may be extracted from these by shaking with dilute sulphuric acid, in which they dissolve. It is also present in tobacco smoke. A number of pyridine bases are present in bone-oil or Dippel's oil, a product obtained by digesting fat extracted bones with water and then distilling. Yield of oil about 6 per cent, and constituents are aliphatic nitriles from  $\text{C}_4$  to  $\text{C}_{18}$ , pyrrole and substituted pyrroles, hydrocarbons of series  $\text{C}_n\text{H}_{2n-4}$  with  $\text{C}_9$ ,  $\text{C}_{10}$  and  $\text{C}_{11}$ , aniline, pyridine and its methyl derivatives, quinoline, phenol, and small amounts of toluene, ethylbenzene and naphthalene.

Mixtures of pyridine bases can readily be obtained from this source. Certain alkaloids (Chap. LVIII) yield pyridine or its derivatives when distilled alone or with alkalis, e.g. chinchonine when distilled with potash yields a dimethyl-pyridine or lutidine. Pure pyridine may be obtained by distilling its carboxylic acid with lime.

Among the more interesting methods by means of which

pyridine and its derivatives have been synthesized are the following:

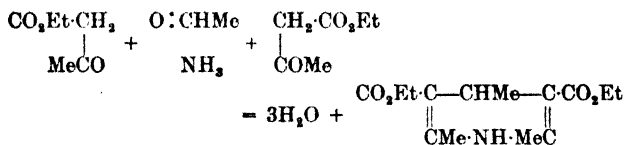
1. When pentamethylene-diamine hydrochloride is strongly heated it yields piperidine, and when this is oxidized with concentrated sulphuric acid at 300° pyridine is formed (*Ladenburg*):



A method very similar to this, which can be employed at much lower temperatures, is the elimination of hydrogen chloride from 5-chloroamylamine,  $\text{CH}_2\text{Cl} \cdot (\text{CH}_2)_3 \cdot \text{CH}_2 \cdot \text{NH}_2$ . This elimination occurs when an aqueous solution of the base is heated on the water-bath; ring formation takes place, and piperidine hydrochloride is formed (*Gabriel*). These two methods are of great importance in deciding the constitution of piperidine, and therefore indirectly that of pyridine.

2. The ammonia derivatives of various unsaturated aldehydes yield pyridine homologues when distilled (p. 154), e.g.  $\beta$ -methyl-pyridine is obtained from acrolein ammonia, and collidine from croton-aldehyde ammonia (*Baeyer*, A., 155, 283, 297).

3. When ethyl acetoacetate is warmed with aldehyde-ammonia, the ester of "Dihydro-collidine-dicarboxylic acid", i.e. ethyl trimethyl-dihydro-pyridine-dicarboxylate is produced (*Hantzsch*) (cf. p. 263):



This loses its two "hydro"-hydrogen atoms when acted on by nitrous acid, and yields ethyl collidine-dicarboxylate,  $\text{C}_5\text{N}(\text{CH}_3)_3(\text{CO}_2\text{Et})_2$ , from which collidine may be obtained by hydrolysis and elimination of carbon dioxide.

If, instead of aldehyde-ammonia, the ammonia compounds

of other aldehydes are used, homologous bases of the type  $C_5H_2N(CH_3)_2(C_nH_{2n+1})$  are formed.

In the above reaction a molecule of the acetoacetic ester may be replaced by one of an aldehyde, when the mono-carboxylic esters of dialkylated dihydro-pyridines are formed, thus:

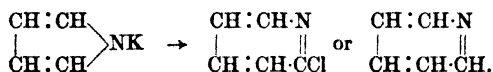


This is a very important synthetical method (*Hantzsch*, A., 215, 1, &c.).

Two methods of obtaining pyridine derivatives, which indicate the relationship of pyridine to quinoline and pyrrole, are:

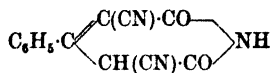
(a) The conversion of quinoline into quinolinic acid or pyridine  $\alpha\beta$ -dicarboxylic acid (p. 687).

(b) The conversion of potassium-pyrrole into chloro-pyridine when heated with chloroform, or into pyridine when heated with methylene-chloride:



The ring constitutional formula (p. 682) is in perfect harmony with the characteristic properties of pyridine and its derivatives, with the number of isomeric derivatives in each case, and also with the synthetical methods of formation.

4. Complex pyridine derivatives are formed by condensing ketones or aldehydes with ethyl cyanoacetate in the presence of ammonia or an amine, e.g. benzaldehyde gives



(G., 1918, 48, ii, 83).

5. Ethyl 2:6-dimethyl-pyridine-3:4-dicarboxylate is readily synthesized by condensing ethyl acetopyruvate,  $CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CO_2Et$ , with ethyl  $\beta$ -aminocrotonate (p. 260) at  $0^\circ$  (B., 1917, 1568; 1918, 150), and from this ester the corresponding dibasic acid, and on oxidation the 2:3:4:6-tetracarboxylic acid are formed, or by elimination of carbon dioxide, 2:6-dimethylpyridine.

To determine the actual position of a substituent it is advisable to convert this into the carboxylic group, e.g. by direct oxidation if it is an alkyl or substituted alkyl group, by replacement by CN if halogen or a sulphonic acid group,

and subsequent hydrolysis. The pyridine carboxylic acids  $\alpha$ ,  $\beta$  and  $\gamma$  (p. 687) are easy to characterize.

Di-derivatives of pyridine containing the same substituent twice can exist theoretically in six isomeric forms, and the six dicarboxylic acids are known ( $\alpha\alpha'$ -,  $\alpha\beta$ -,  $\alpha\gamma$ -,  $\alpha\beta'$ -,  $\beta\gamma$ -, and  $\beta\beta'$ -) (see p. 688).

The methylpyridines (picolines) are isomeric with aniline.

**Pyridine**,  $C_5H_5N$  (*Anderson*, 1851), may be prepared from bone-oil, and can be obtained pure by heating its carboxylic acid with lime; the ferrocyanide is especially applicable for its purification, on account of its sparing solubility in cold water. It is also found in the ammonia of commerce. Pyridine is a liquid of very characteristic odour, miscible with water, and boiling at  $115^\circ$ . It is used as a remedy for asthma, and also for mixing with spirit of wine in order to render the latter duty-free. When sodium is added to its hot alcoholic solution, or when solutions of its salts are electrolysed, hydrogen is taken up and piperidine,  $C_5H_{11}N$ , formed (*Ladenburg* and *Roth*).

The pyridine ring is extremely stable, but when heated strongly with hydriodic acid, pyridine is converted into normal pentane.

The ammonium iodides, e.g.  $C_5H_5N$ ,  $CH_3I$ , give a characteristic pungent odour when heated with potash, a fact which may be made use of as a test for pyridine bases; it depends upon the formation of alkylated dihydro-pyridines, e.g. **di-hydro-methyl-pyridine**,  $C_5H_6N(CH_3)$  (*Hofmann*, B., 1881, 1497).

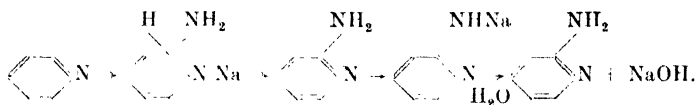
Pyridine is polymerized by the action of metallic sodium to **dipyridine**,  $C_{10}H_{10}N_2$  (an oil, b.-pt.  $286^\circ$ – $290^\circ$ ), with the simultaneous production of *p*-**dipyridyl**,  $C_5H_4N \cdot C_5H_4N$  (long needles, m.-pt.  $114^\circ$ ), a compound corresponding with diphenyl (*Chap.* XXVII); both of these yield iso-nicotinic acid when oxidized. An isomeric *m*-**dipyridyl** has also been prepared, which gives nicotinic acid when oxidized, and 2:2'-pyridyl is formed by dehydrogenating pyridine with  $FeCl_3$  at  $300^\circ$  and 100 atm. pressure.

Pyridine can be brominated but not nitrated; it can also be sulphonated with the formation of  $\beta$ -pyridine-sulphonic acid,  $C_5H_4N \cdot (SO_3H)$ , which with potassium cyanide yields  $\beta$ -**cyano-pyridine**,  $C_5H_4N \cdot CN$ , or by fusion with potash,  $\beta$ -hydroxypyridine.

**2-Amino-** and **2:6-diamino-**derivatives are formed by the

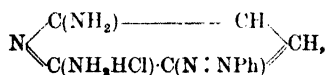


action of sodamide on pyridine and subsequent treatment with water. The reaction, in the case of 2-amino-pyridine, can be represented as



They can be diazotized in the same way as aniline, and give rise to azo-dyes.

An azo-compound of medicinal importance is **pyridium**,



from benzene diazonium chloride and the 2:6-diamino-pyridine.

The three **hydroxy-pyridines**,  $\text{C}_5\text{H}_4\text{N}(\text{OH})$  ( $\alpha$ -,  $\beta$ -,  $\gamma$ -), are best prepared by the elimination of carbon dioxide from the respective hydroxy-pyridine-carboxylic acids. The melting-points are respectively:  $\alpha$ ,  $107^\circ$ ;  $\beta$ ,  $124^\circ$ ;  $\gamma$ ,  $148^\circ$ . They possess the character of phenols, and are coloured red or yellow by ferric chloride. As in the case of phloroglucinol, so here also there is a tertiary as well as a secondary form to be taken into account, the former reminding one of the lactams and the latter of the lactims; for instance,  $\gamma$ -hydroxy-pyridine may

have either the "phenol" formula  $\text{C}_2\text{H}_2 \begin{array}{c} \diagup \text{C}(\text{OH}) \\ \diagdown \text{N} \end{array} \text{---} \text{C}_2\text{H}_2$  or the "pyridone" formula  $\text{C}_2\text{H}_2 \begin{array}{c} \diagup \text{CO} \\ \diagdown \text{NH} \end{array} \text{---} \text{C}_2\text{H}_2$ , the latter of the two

representing a keto-dihydro-pyridine. The two methyl ethers, methoxy-pyridine and methyl-pyridone, corresponding with the phenol and pyridone formulæ, are both known, and differ considerably in properties (M., 1885, 307, 320; B., 1891, 3144).

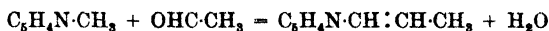
The hydroxy- and amino-compounds are more readily substituted than pyridine.

**Homologues of Pyridine** (cf. *Ladenburg*, A., 247, 1).—**Methyl-pyridines** or **picolines**,  $\text{C}_5\text{H}_4\text{N}(\text{CH}_3)$ . **Dimethylpyridines** or **lutidines** and **trimethyl-pyridines** or **collidines** are present in bone-oil, and on oxidation yield the corresponding carboxylic acids. All have pungent odours. The boiling-points

are  $\alpha$  129°,  $\beta$  142°,  $\gamma$  142°–144°,  $\alpha\alpha'$  142°,  $\alpha\gamma$  157°,  $\beta\gamma$  164°,  $\alpha\alpha'\gamma$  171°–172°. The  $\beta$ -compound is obtained from acrolein-ammonia (p. 154), and also when strychnine is heated with lime, or when trimethylene-diamine hydrochloride is distilled.

The *s*-collidine,  $\alpha\alpha'\gamma$ , is formed by condensing ethyl acetate and aldehyde-ammonia or from acetamide and acetone at 250°. Similarly, acetophenone and benzamide yield *s*-triphenylpyridine (C. R., 1916, 162, 876).

**Propyl- and isopropyl-pyridines**,  $C_5H_4N(C_3H_7)$ , related to coniine, are prepared by heating pyridine with the alkyl iodides. **Conyryne**,  $C_8H_{11}N$  (liquid, b.-pt. 166°–168°), which is formed when coniine,  $C_8H_{17}N$ , is heated with zinc dust, and which yields coniine again when treated with hydriodic acid, is  $\alpha$ -normal-propyl-pyridine.  **$\alpha$ -Allyl-pyridine**,  $C_5H_4N(C_3H_5)$ , is formed when  $\alpha$ -picoline is heated with aldehyde:



Reduction transforms it into inactive coniine (b.-pt. 189°–190°).

**Pyridine-carboxylic Acids** (Weber, A., 1887, 241, 1).—The **pyridine-mono-carboxylic acids**,  $C_5H_4N(CO_2H)$ , are formed by the oxidation of all mono-alkyl derivatives of pyridine, i.e. from methyl-, propyl-, phenyl-, &c., pyridines; also from the pyridine-dicarboxylic acids by the elimination of one of the carboxyl groups, just as benzoic may be got from phthalic acid. The carboxyl which is in closest proximity to the nitrogen is the first to be eliminated. Nicotinic acid is also produced by the oxidation of nicotine. The acids unite in themselves the characters of the basic pyridine and of an acid, and are therefore comparable with glycine. They yield salts with HCl, &c., and double salts with  $HgCl_2$ ,  $PtCl_4$ , &c.; on the other hand, they form metallic salts as acids, those with copper being frequently made use of for the separation of the acids.

(For constitution see Skraup and Cobenzl, M., 1883, 436.)

The  $\alpha$ -,  $\beta$ -, and  $\gamma$ -acids are known as **picolinic acid**, **nicotinic acid**, and **iso-nicotinic acid**. All three acids (and also the  $\beta\gamma$ -dicarboxylic acid) readily lose nitrogen as ammonia when acted upon by sodium amalgam, yielding aliphatic unsaturated acids (Weidel, M., 1890, 501). The respective melting-points are 135°, 231° and 309° (in sealed tube).

The constitution of nicotinic acid follows from its relationship to quinoline. Quinoline on oxidation yields pyridine  $\alpha\beta$ -dicarboxylic acid, the constitution of which follows from

the constitution of quinoline. When heated, the dibasic acid loses carbon dioxide, yielding a monobasic acid which is not identical with picolinic acid (which can be shown to be the  $\alpha$ -acid), and therefore it must be pyridine  $\beta$ -carboxylic acid.

*Pyridine-dicarboxylic acids,  $C_5H_3N(CO_2H)_2$*

$\alpha$ - $\beta$ -	= Quinolinic acid	..	..	..	M.-pt. 190°.
$\alpha$ - $\gamma$ -	= Lutidinic acid	..	..	..	M.-pt. 235°.
$\alpha$ - $\alpha'$ -	= Dipicolinic acid	..	..	..	M.-pt. 226°.
$\alpha$ - $\beta'$ -	= Iso-cinchomeric acid	..	..	..	M.-pt. 236°.
$\beta$ - $\beta'$ -	= Dinicotinic acid	..	..	..	M.-pt. 323°.
$\beta$ - $\gamma$ -	= Cinchomeric acid	..	..	..	M.-pt. 266°.

Quinolinic acid, which crystallizes in short glistening prisms, is the analogue of phthalic acid, and is obtained by the oxidation of quinoline, just as phthalic acid from naphthalene; cinchomeric and iso-cinchomeric acids are obtained by the oxidation of cinchonine and quinine.

**Hydro-pyridines.**—According to theory, hexa-, tetra-, and dihydro-pyridines may exist. The first of these receive the generic name of "piperidines", e.g. pipercoline,  $C_5H_{10}N(CH_3)$ , lupetidine,  $C_5H_9N(CH_3)_2$ , and copellidine,  $C_5H_8N(CH_3)_3$ ; while the tetrahydro-compounds are termed "piperideins".

**Piperidine**,  $C_5H_{11}N$  (Wertheim, Rochleder, 1850), is a colourless liquid of peculiar odour, slightly resembling that of pepper, and of strongly basic properties yielding crystalline salts. It dissolves readily in water and alcohol, and boils at 106°.

It occurs in pepper in combination with piperic acid,  $C_{12}H_{10}O_4$  (p. 533), in the form of the alkaloid **piperine**,  $C_{17}H_{19}NO_3$ ,  $C_5H_{10}N \cdot C_{12}H_9O_3$ , i.e. piperyl-piperidine, which crystallizes in prisms, melting at 129°; from this latter it may be prepared by boiling with alkali.

(For its formation from pyridine and from pentamethylene-diamine see pp. 227, 681, 683.)

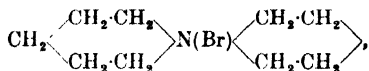
Piperidine is a true secondary amine; its imino-hydrogen is replaceable by alkyl and acyl radicals. When its vapour, mixed with that of alcohol, is led over zinc dust, homologous (ethylated) piperidines are formed.

When methylated, piperidine yields, as a secondary base, in the first instance, tertiary **N-methyl-piperidine**,  $C_5H_{10}N(CH_3)$ , and then with a further quantity of methyl iodide an ammonium iodide, **dimethylpiperidonium iodide**. The corresponding hydroxide does not decompose in the usual manner when

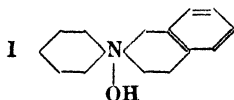
distilled, but yields water and an aliphatic base, "dimethyl piperidine",  $C_7H_{15}N$  or  $CH_2:CH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NMe_2$ .

The latter forms a quaternary iodide, the hydroxide of which, when distilled, gives trimethylamine and piperylene,  $CHMe:CH:CH:CH_2$ . This process of converting bases into their quaternary ammonium salts and the distillation of these with alkalis is usually termed **exhaustive methylation**, and is largely used for preparing unsaturated compounds (cf. also chapter on Alkaloids).

The method of exhaustive methylation has also been used for ascertaining the relative stabilities of certain ring systems (*v. Braun*, B., 1916, 2629; 1922, 3818). The method is based on the use of a compound containing two different ring systems, e.g. pyrrolidylpiperidonium bromide,



and determining which ring is ruptured under the influence of alkalis. When examined in this way piperidyl-tetrahydro-isoquinolonium hydroxide, I—from tetrahydro-isoquinoline,



1: 5-dibromopentane and alkali—yields 1-*o*-vinylbenzyl-piperidine,  $C_5H_{10}N \cdot CH_2 \cdot C_6H_4 \cdot CH:CH_2$ , indicating that under these conditions the tetrahydro-isoquinoline ring is ruptured more readily than the piperidine ring. As the result of numerous experiments the following has been shown to be the order of increasing stability of N rings: tetrahydro-isoquinoline, dihydro-isoindole, pyrrolidine, piperidine, dihydro-indole, tetrahydroquinoline.

Cyanogen bromide (p. 307) can also be used for producing fission of N rings, and in this case also the order of stability is practically the same, with the exception of the dihydroindole

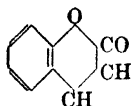
ring  $C_6H_4 \begin{array}{c} \text{CH}_2 \diagup \\ \text{NMe} \diagdown \end{array} CH_2$ , which, although stable when treated

by the process of exhaustive methylation, is readily ruptured by cyanogen bromide (*ibid.* 1918, 96, 255).

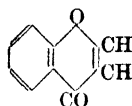
## XLIV. QUINOLINE AND ACRIDINE GROUPS

## A. Quinoline Group

The quinoline group comprises the compounds formed by the condensation of a benzene nucleus with a heterocyclic six-membered ring. The best-known examples are:



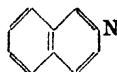
Coumarin  
(benzene + 1:2 pyrone)



Chromone  
(benzene + 1:4 pyrone)



Quinoline  
(benzene + pyridine)



Iso-quinoline  
(benzene + pyridine)

## 1. CHROMONE GROUP

**Chromones.**—The coumarins and chromones are closely allied, and both types of compounds are sometimes formed in the same reaction. Coumarin has already been described under *o*-hydroxycinnamic acid, of which it is the lactone. *Chromone*, prepared by *Ruhemann* and *Stapleton* (J. C. S., 1900, 1185) melts at 85°, and the parent substance **chromane**,

$\text{C}_6\text{H}_4 \begin{array}{l} \diagup \text{O}-\text{CH}_2 \\ \diagdown \text{CH}_2 \cdot \text{CH}_2 \end{array}$ , can be prepared (a) by condensing trimethyl-

ylene chlorhydrin with sodium phenoxide to form phenyl  $\gamma$ -hydroxypropyl ether,  $\text{C}_6\text{H}_5 \cdot \text{O} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{OH}$ , and heating this with zinc chloride, or (b) by heating  $\gamma$ -bromopropyl phenyl ether (from trimethylene dibromide and sodium phenoxide) with zinc. Yield, 65 per cent. An attempt to pre-

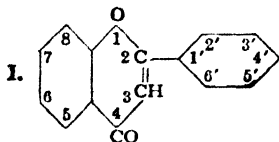
pare **chromene**,  $\text{C}_6\text{H}_4 \begin{array}{l} \diagup \text{O}-\text{CH} \\ \diagdown \text{CH}_2 \cdot \text{CH} \end{array}$ , from *o*-allylphenol by con-

version into the acetate, then into the dibromide, and the

action of alcoholic potash on this, gave the isomeric methylene-coumaran,  $C_6H_4 \begin{array}{c} \diagup O \diagdown \\ \diagdown CH_2 \diagup \end{array} C:CH_2$  (Chap. XLI) (*Adams and*

*Rindfuss*, J. A. C. S., 1919, 648).

3:7-Dihydroxy chromone is formed by the atmospheric oxidation of brazilin, a complex compound obtained from brazilwood.



Chromone and its 2-phenyl-derivative, **flavone I**, are the parent substances of important yellow dyes found in the vegetable kingdom. All of these contain hydroxy groups and are found in the form of glycosides.

Hydroxy compounds of 3-phenyl-chromone are termed **iso-flavones**, and derivatives of 3-hydroxy-flavone are **flavonols** (cf. Chap. LXIV, B.).

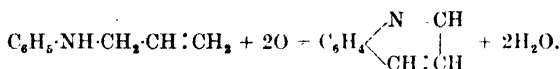
Resacetophenone (2:4-dihydroxy-acetophenone) with sodium acetate and acetic anhydride yields 7-acetoxy-3-acetyl-2-methylchromone and many other hydroxy-aceto-phenones behave in the same way, but not those containing *ortho* OH groups (*Kostanecki* and others, B., 1901, 107). The method has been extended to the naphthyl series (J. C. S., 1931, 1165, 2591), and also to hydroxy-propiophenones and butyrophenones (*ibid.* 1245, 1877).

## 2. QUINOLINE AND ITS DERIVATIVES

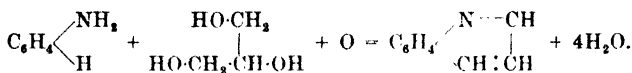
**Quinoline** (for structure cf. p. 694) bears the same relationship to naphthalene that pyridine does to benzene, its molecule consisting of condensed benzene and pyridine nuclei. It occurs, together with derivatives, in both coal-tar and bone-oil, and may be obtained by heating certain alkaloids with potash, e.g. cinchonine yields quinoline itself (*Gerhardt*, 1842), and quinine gives methoxy-quinoline.

Among the various syntheses of quinoline and its derivatives the following may be noted:

1. The first synthesis (*Koenigs*) was by the oxidation of allyl-aniline by passing its vapour over heated lead oxide:

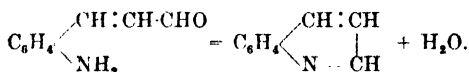


2. In the common synthesis (*Skraup*, B., 1887, 1902) aniline is heated with glycerol and sulphuric acid in presence of nitrobenzene or arsenic acid as oxidizing agent:

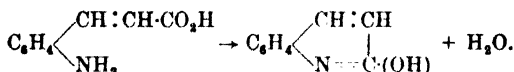


The intermediate products are probably acrolein and acrolein-aniline,  $\text{C}_6\text{H}_5\cdot\text{N}:\text{CH}\cdot\text{CH}:\text{CH}_2$ . The homologues and analogues of aniline yield homologues and analogues of quinoline by corresponding reactions; when a naphthyl-amine is used, the more complicated naphtho-quinolines are formed.

3. *Baeyer* and *Drewson* (B., 1883, 2207) obtained quinoline by the elimination of the elements of water from *o*-amino-cinnam-aldehyde:

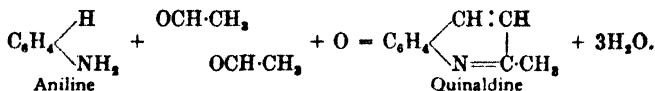


If *o*-amino-cinnamic acid is used, carbostyryl ( $\alpha$ -hydroxy-quinoline, p. 695) is obtained (*Baeyer*):



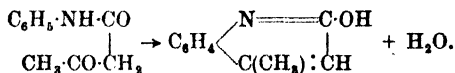
4. When aniline is heated with aldehyde (paraldehyde) and hydrochloric acid,  $\alpha$ -methyl-quinoline (quinaldine) is obtained (*Doebner* and *v. Miller*).

In this reaction ethylidene-aniline is formed as an intermediate product (B., 1891, 1720; 1892, 2072):

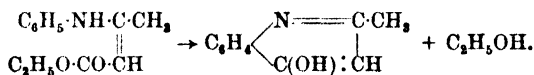


Here, again, various other primary arylamines may be used instead of aniline, and other aldehydes or ketones instead of paraldehyde (B., 1885, 3361; 1886, 1394).

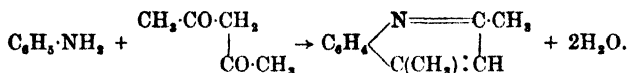
5. Aniline and acetoacetic acid combine together at temperatures above  $110^{\circ}$  to aceto-acetanilide,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_5$ , from which 4-methyl-2-hydroxy-quinoline ("methyl-carbostyryl") is formed by the elimination of water (*Knorr*, A., 1886, 236, 75):



Aniline can also react with acetoacetic ester below  $100^{\circ}$ , yielding **ethyl  $\beta$ -phenyl-amino-crotonate**,  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{C}(\text{CH}_3):\text{CH}\cdot\text{CO}_2\text{C}_2\text{H}_5$ , which yields 2-methyl-4-hydroxy-quinoline when heated (*Conrad and Limpach*, B., 1887, 944):

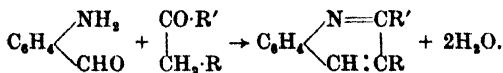


$\beta$ -Diketones and other compounds closely related to acetoacetic ester also condense with aniline. In place of  $\beta$ -diketones, mixtures of ketones and aldehydes, or mixtures of aldehydes which would yield  $\beta$ -diketones or  $\beta$ -ketonic aldehydes if condensed together (*C. Beyer*, B., 1887, 1767), can be employed. With acetyl-acetone 2:4-dimethyl-quinoline is formed (B., 1899, 3228):



These reactions are nearly allied to those already spoken of under 4.

6. *o*-Amino-benzaldehyde condenses with aldehydes and ketones under the influence of dilute caustic soda solution, yielding quinoline derivatives (*Friedländer*, B., 1882, 2574; 1883, 1833; 1892, 1752). With aldehyde quinoline itself results, and with acetone quinaldine:



Acetophenone, acetoacetic ester, malonic ester, diketones, &c., also react in a similar way.

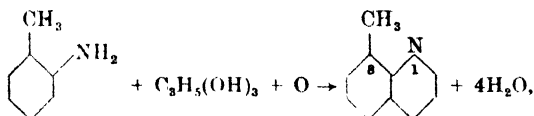
*Constitution.*—The above modes of formation (especially 3 and 6) show that quinoline is an ortho-di-substituted-derivative





seven mono-substituted derivatives of quinoline are in each case theoretically possible. As a matter of fact, all seven quinoline-monocarboxylic acids have been prepared.

The position of the substituents follows: (a) from the nature of the oxidation products, e.g. B-quinoline-carboxylic acid (i.e. an acid in which the carboxyl is attached to the benzene nucleus) yield a pyridine-dicarboxylic acid, while a Py-quinoline-carboxylic acid (in which the carboxyl is linked to the pyridine nucleus) yields a pyridine-tricarboxylic acid; (b) from the synthesis of the compound in question. The methyl-quinoline, for instance, which is obtained from *o*-toluidine by the *Skraup* synthesis must be the 8-methyl-quinoline:



whilst *m*-toluidine must yield a 7- or 5-, and *p*-toluidine a 6-methyl quinoline.

**Quinoline** (*Runge*, 1834) is a colourless strongly refracting liquid of a peculiar and very characteristic odour. It boils at  $239^\circ$ , is a mono-acid base, forms a sparingly soluble dichromate,  $(\text{C}_7\text{H}_7\text{N})_2$ ,  $\text{H}_2\text{Cr}_2\text{O}_7$ , and is used as an antifebrile. As a tertiary base it yields **quinolonium** salts (*Roser*, A., 1893, 272, 221).

Nascent hydrogen transforms it first into **dihydro-quinoline**,  $\text{C}_8\text{H}_9\text{N}$ , which melts at  $161^\circ$ , and then into **tetrahydro-quinoline**,

$\text{C}_8\text{H}_{11}\text{N}$ , =  $\text{C}_6\text{H}_4 \begin{array}{l} \text{NH} \cdot \text{CH}_2 \\ | \\ \text{CH}_2 \cdot \text{CH}_2 \end{array}$ , a liquid boiling at  $245^\circ$ . The pyri-

dine is more readily hydrogenated than the benzene ring, as both of these yield nitrosamines and can be alkylated, and are secondary bases. The tetrahydro-compound exerts a stronger antifebrile action than the mother substance, especially in the form of its ethyl derivative, **caïrolin**.

**Quinoline decahydride**,  $\text{C}_{10}\text{H}_{17}\text{N}$ , forms crystals of a narcotic, coniine-like odour, melts at  $48^\circ$ , and boils at  $204^\circ$ .

Halogen derivatives of quinoline and nitro-quinolines have been prepared by the *Skraup* reaction, &c.; and, from the reduction of the latter, amino-quinolines,  $\text{C}_8\text{H}_6\text{N}(\text{NH}_2)$ . The quinoline-sulphonic acids yield cyano-quinolines with potassium cyanide, and hydroxy-quinolines when fused with potash.

**2-Hydroxy-quinoline**, *carbostyrl*, is a quinoline hydroxylated

in the pyridine nucleus (see p. 692, mode of formation 3). It crystallizes in colourless needles, melts at  $198^{\circ}$ , and is soluble in alkali, from which it is again thrown down by carbonic acid. Its constitution follows from its formation from *o*-amino-cinnamic acid (p. 523).

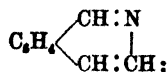
**Quinaldine**, 2-methyl-quinoline,  $C_{10}H_9N$ , is contained in coal-tar. It is a colourless liquid of quinoline odour, and boils at  $246^{\circ}$ . When oxidized with chromic acid it yields a quinoline derivative, with permanganate a pyridine-tricarboxylic acid.

The hydrogen of the methyl group readily enters into reaction; quinaldine condenses with phthalic anhydride to produce the dye, **quinoline-yellow**,  $C_{10}H_7N(CO)_2C_6H_4$ , the disulphonic acid of which is **quinoline-yellow S**. A mixture of quinoline and quinaldine is transformed into the (unstable) blue dyes, the **cyanines**, when alkylated and treated with caustic potash. These are used as sensitizers for photographic plates (cf. Chap. LIX, F.).

**Quinoline-carboxylic Acids**.—**Cinchoninic acid**, *quinoline-4-carboxylic acid*,  $C_9H_6N(CO_2H)$ , which is obtained by the oxidation of cinchonine with permanganate of potash, crystallizes in needles or prisms and melts at  $254^{\circ}$ . From it is derived **quinic acid**, 6-methoxy-quinoline-4-carboxylic acid,  $C_9H_5N(OCH_3) \cdot CO_2H$ , which is obtained by oxidizing quinine with chromic acid; it forms yellow prisms, melting at  $280^{\circ}$ . **Quinoline-2:3-dicarboxylic acid**, or *acridinic acid*, is formed by the oxidation of acridine.

### 3. ISO-QUINOLINE

**Iso-quinoline**, an isomer of quinoline, occurs along with the latter in coal-tar. It is a solid, melts at  $23^{\circ}$ , and boils at  $240^{\circ}$ . Since oxidation converts it into cinchomeronic acid on the one hand and phthalic acid on the other it possesses the constitution:



and this is supported by the following syntheses\*:

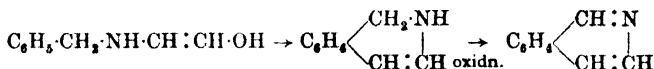
(1) Homophthalic acid, I, in which the substituents are in the *o*-position, yields the cyclic imide by heating the ammonium

\* For synthesis from  $\beta$ -naphthaquinone see B., 1892, 1138, 1493; 1894, 198.

salt, and this with phosphorus oxychloride reacts as the enol, II, yielding dichloro-iso-quinoline, which is reduced by hydriodic acid and red phosphorus to iso-quinoline.

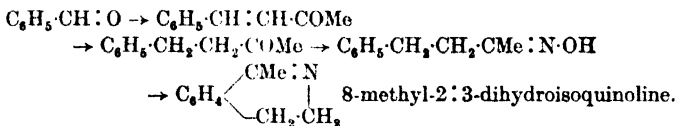


(2) From the enolic form of benzylaminoacetaldehyde hydrochloride and fuming sulphuric acid:

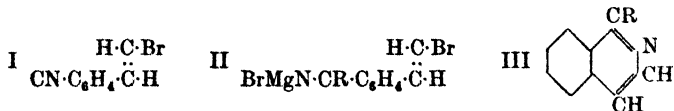


(E. Fischer, B., 1893, 764).

(3) A simple synthesis of iso-quinoline derivatives is as follows: An unsaturated ketone is formed by condensing an aromatic aldehyde with acetone; this is reduced and then converted into the oxime, from which, by the *Beckmann* rearrangement, dihydroisoquinolines are formed together with other products (B., 1916, 675):



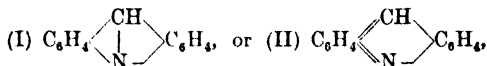
(4) 1-Alkylisoquinolines can be synthesized from *allo-o*-cyanocinnamic acid; this with bromine followed by water gives *trans*- $\omega$ -bromo-*o*-cyano-styrene, I, which can react with *Grignard* compounds  $\text{R}\cdot\text{Mg}\cdot\text{Br}$ , yielding II, and this on heating gives III.



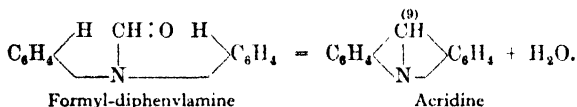
## B. The Acridine Group

**Acridine**,  $\text{C}_{13}\text{H}_9\text{N}$  (*Graebe* and *Caro*), is a basic constituent of the crude anthracene of coal-tar, and also of crude diphenylamine. It crystallizes in colourless needles, may be sublimed, and is characterized by an intensely irritating action upon the epidermis and the mucous membrane, and also by the greenish-blue fluorescence shown by dilute solutions of its salts.

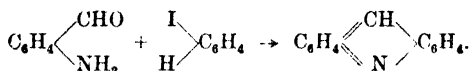
Acridine stands in the same relationship to anthracene that pyridine does to benzene or quinoline to naphthalene. It may be regarded as anthracene in which one of the CH groups of the middle ring is replaced by N. The constitutional formula,



is based (a) upon the oxidation of acridine to quinoline-2:3-dicarboxylic acid, and to pyridine tetracarboxylic acid—the *p*-union between C and N in I becomes ruptured during the oxidation; (b) upon its synthesis from diphenylamine and formic acid, or formyl-diphenylamine,  $(\text{C}_6\text{H}_5)_2\text{N}\cdot\text{CHO}$ , with zinc chloride (*Bernthsen*, A., 224, 1):



It is also obtained when the vapour of *o*-tolyl-aniline is passed through a red-hot tube. An interesting synthesis is by boiling *o*-aminobenzaldehyde and iodobenzene in nitrobenzene solution with  $\text{Na}_2\text{CO}_3$  and Cu powder (*B.*, 1917, 1306):



Acridine is a tertiary base, and as such combines with alkyl iodides, yielding **acridonium iodides**. It is a much feebler base than quinoline, and on reduction readily forms a dihydro-derivative, which is not basic.

**9-Methyl- and butyl-acridines, phenyl-acridine, and naphtho-acridines** (i.e. acridines which contain  $\text{C}_{10}\text{H}_8$  instead of  $\text{C}_6\text{H}_4$ ) have all been prepared synthetically.

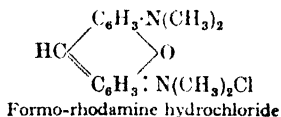
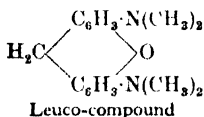
Acridine, like anthracene, is a chromogene, and gives rise to the acridine dyes (*Chap. LIX, F.*).

The oxygen analogue of dihydro-acridine,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CH}_2 \diagdown \\ | \\ \text{NH} \end{array} \text{C}_6\text{H}_4$ ,  
is **diphenylene-methane oxide, or xanthene**,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CH}_2 \diagdown \\ | \\ \text{O} \end{array} \text{C}_6\text{H}_4$ ,

a decomposition product of aluminium phenoxide, also obtained by distilling euxanthone over zinc dust. It crystallizes in plates, and melts at  $98.5^{\circ}$ . It is on the one hand the mother substance

of **xanthone**,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{O} \diagup \end{array} \text{C}_6\text{H}_4$ , and its derivative **euxanthone** or *dihydroxy-xanthone*,  $\text{OH}\cdot\text{C}_6\text{H}_3 \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{O} \diagup \end{array} \text{C}_6\text{H}_3\cdot\text{OH}$ , and, on the

other hand, of the rhodamines and fluoresceins (Chap. XXX, A4). Its **tetramethyl-diamino** derivative is formed by the condensation of formaldehyde with *m*-dimethylamino-phenol to tetramethyl-diamino-dihydroxy-diphenyl-methane and subsequent elimination of water (ring formation), and is the leuco-compound of **formo-rhodamine** or *pyronine*,  $\text{C}_{17}\text{H}_{19}\text{N}_2\text{OCl}$ , into which it passes upon oxidation and production of quinonoid linking:



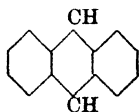
#### XLV. SIX-MEMBERED HETEROCYCLIC COMPOUNDS WITH NOT MORE THAN FOUR CARBON ATOMS IN RING. AZINES, ETC.

A number of six-membered heterocyclic compounds, containing four carbon and two other atoms, are known, e.g. **par-oxazine**, with 4C, 1O, and 1N, the O and N in the *p*-position.

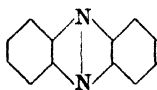
A derivative of this is **morpholine**,  $\text{O} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \diagdown \\ \diagdown \text{CH}_2\text{CH}_2 \diagup \end{array} \text{NH}$ . Simi-

larly, **thiazines** (4C, 1S, 1N) and **diazines** (4C, 2N) are known; and these are the parent substances of numerous important dyes. The majority of these dyes are not simple derivatives of oxazines, thiazines, or diazines, but are derived from condensed benzene and oxazine, or benzene and diazene nuclei, and may be compared with anthracene. For example, **phena-**

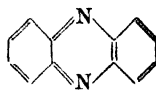
**zine** is anthracene in which two CH-groups have been replaced by two N-radicals:



Anthracene

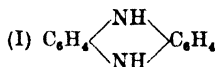


or

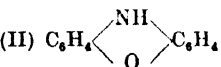


Phenazine

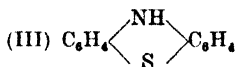
dihydro-phenazine corresponds with dihydro-anthracene, and phenoxazine with dihydro-anthracene in which one  $\text{CH}_2$  has been replaced by O and another by NH, e.g.:



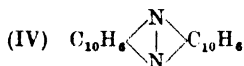
Dihydro-phenazine



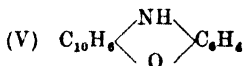
Phenoxazine

Phenthiazine  
(thio-diphenylamine)

Further, the benzene nuclei may be replaced by those of naphthalene, with the formation of:

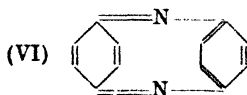


Naphthazine



Naphtho-phenoxazine

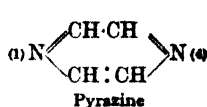
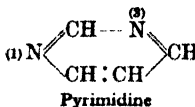
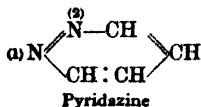
An isomeride obtained from *p*-chloraniline,  $\text{ZnCl}_2$  and  $\text{AlCl}_3$ , is represented by formula VI, and contains a ring with 10 atoms.



The compounds (I-III) of the type of dihydro-anthracene are the leuco-compounds of dyes when they contain an amino-(alkylamino-) or hydroxy-group in the *para*-position to the nitrogen. The dyes themselves are derived from amino- or hydroxy-phenazines (see Chap. LIX, H.).

### THE DIAZINES

The three simple diazines are:



**Pyridazine** is a colourless liquid, b.-pt.  $208^{\circ}$ , is miscible with water, has an odour of pyridine, and forms soluble salts (Preparation, B., 1895, 451; Derivatives, Annales, 1914, ix, 2, 403).

**Pyrimidine** can be obtained from barbituric acid and from methyluracil (p. 324); it forms colourless crystals, m.-pt.  $22^{\circ}$  and b.-pt.  $124^{\circ}$ . The pyrimidine ring is met with in uric acid and in most purine derivatives (cf. B., 1901, 3248).

Substituted pyrimidines are formed on hydrolysing proteins. (For study cf. *Johnson* and co-workers, J. A. C. S., 1924–1938.) They are formed by the action of guanidine (p. 317) on hydroxy-methylene ketone (B., 1930, 2601).

**Pyrazine** forms colourless prisms, m.-pt.  $47^{\circ}$ , b.-pt.  $118^{\circ}$ , and is basic (J. pr. [ii], 51, 449). **Dimethylpyrazine**, *Ketin*, is present in crude amyl alcohol, and can be obtained by the reduction of isonitrosoacetone or by condensation of aminoacetone. **Tetraphenylpyrazine** is readily obtained from benzoin. Hexahydropyrazine or **piperazine** is diethylene-diamine and is a solid, m.-pt.  $104^{\circ}$ , b.-pt.  $145^{\circ}$ , and is used in medicine as a uric acid eliminant. It is manufactured by the action of ethylene bromide on aniline, converting the diphenyldiethylene-

diamine  $\text{C}_6\text{H}_5\text{--N} \begin{array}{c} \text{C}_2\text{H}_4 \\ \text{C}_2\text{H}_4 \end{array} \text{--NC}_6\text{H}_5$  into its di-*p*-nitroso-derivative and hydrolysing this to phenol and piperazine.

Of the compounds formed by the union of a benzene and a diazine nucleus the most important is **quinoxaline**,

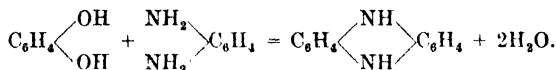
$\text{C}_6\text{H}_4 \begin{array}{c} \text{N}:\text{CH} \\ | \\ \text{N}:\text{CH} \end{array}$ , which is obtained from *o*-phenylene-diamine and

glyoxal. Substituted quinoxalines are formed by condensing  $\alpha$ -diketones,  $\alpha$ -ketonic acids, &c., with *o*-phenylene-diamines. Of more importance is the group of compounds containing two benzene nuclei condensed with one diazine ring, e.g. phenazine.

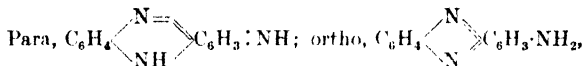
**Phenazine**, or *azo-phenylene* (p. 700), is obtained by the distillation of barium azo-benzoate, or by leading the vapour of aniline through red-hot tubes; also from nitrobenzene, aniline, and sodium hydroxide at  $140^{\circ}$ , or by the oxidation of its hydro-compound (see below). It crystallizes in beautiful, long, bright-yellow needles melting at  $171^{\circ}$ , and can be readily sublimed. It is only sparingly soluble in alcohol, but readily



in ether, and also dissolves in concentrated sulphuric acid to a red solution; the alcoholic solution yields a green precipitate on the addition of stannous chloride. When reduced with ammonium sulphide it yields the colourless hydro-compound, **di-hydro-phenazine**,  $C_{12}H_{10}O_2$ , which may be obtained synthetically by heating catechol with *o*-phenylene-diamine:

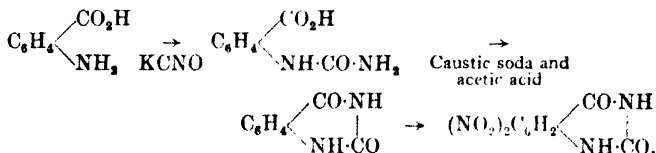


The entrance of hydroxy- or amino-groups into these azines converts them into dyes. In accordance with modern views of the quinonoid structure of dyes these derivatives are usually given ortho or para quinonoid formulæ:



and similarly for hydroxy derivatives. For the more important of these dyes cf. Chap. LIX, H.

An indicator,  $(NO_2)_2C_6H_2 \begin{array}{c} \diagup CO \cdot NH \\ \diagdown NH \cdot CO \end{array}$ , a pyrimidine derivative, can be obtained from anthranilic acid by the following series of reactions:



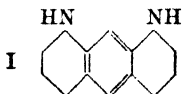
It gives a greenish-yellow colour with hydron concentrations of  $10^{-8}$ ; below  $10^{-6}$  it is colourless (J. A. C. S., 1916, 1606).

#### PHENOXAZINES AND PHENTHIAZINES

**Phenoxazine** (p. 700) is obtained by heating catechol with *o*-aminophenol. **Phenthiazine** (p. 700) is formed by heating phenylamine and sulphur with  $AlCl_3$  or I, and is a powerful insecticide. For phenoxazine dyes see Chap. LIX, H.

Derivatives of octahydrodipyridobenzene I are known (Helv., 1936, 439), and can be obtained by condensing 1 : 3-

phenylenediacrylic acid,  $\text{C}_6\text{H}_4(\text{CH}:\text{CH}\cdot\text{CO}_2\text{H})$ , reducing, nitrating to 4:6-dinitro-compound, reducing to diamine, heating to  $260^\circ$  to produce ring closure and the cyclic diketone reduced with P and I:



## XLVI. CO-ORDINATION COMPOUNDS

### A. Co-ordinated Metallic Complexes

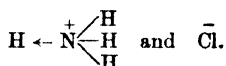
This was the term given by *Werner* to certain types of additive compounds and complex salts comprising the metallic amines, aquo-compounds, oxalates and cyanides. *Werner* pointed out the difference in combining power between an atom attached to only one type of element and the same atom attached to two or more types, e.g.  $\text{NH}_3$  or  $\text{NCl}_3$  compared with  $\text{NH}_4\text{Cl}$ ,  $\text{PtCl}_4$  and  $\text{K}_2\text{PtCl}_6$ ,  $\text{Fe}(\text{CN})_3$  and  $\text{K}_4\text{Fe}(\text{CN})_6$ .

He pointed out that, in the case of salts, certain atoms or groups appeared to be in an outer sphere—what are now termed the simple cation or anion, and that in the remainder of the molecule (the other more complex ion) the metallic atom was attached to 4 or 6 other atoms, radicals, complexes or molecules (e.g.  $\text{NH}_3$  or  $\text{H}_2\text{O}$ ). This number is termed the co-ordination number, and is always 4, 6 or occasionally 8. *Werner* found it difficult to give structural formulæ for these compounds based on the usual valencies of the different atoms and groups, and therefore introduced the idea of **subsidiary valencies** which he denoted by dotted lines. The structure of these co-ordination compounds or ions is readily explained in terms of the electronic structure of atoms (pp. 14 et seq.), and *Werner's* subsidiary valencies become co-ordinate linkings. Take the formation of ammonium chloride by the combination of ammonia and hydrochloric acid. The electron structure of the nitrogen atom is 2:2, 2, 1, and to attain the neon structure 2:2, 2, 4 it requires 3 more electrons, and these it obtains

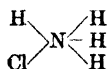
by sharing an electron from each of 3 hydrogen atoms, so ammonia is



with still a pair of unshared (lone) electrons. The hydrogen chloride is ionized  $\text{H}^+$  and  $\text{Cl}^-$ , i.e. the hydrogen atom is deprived of its one electron, and to attain the helium structure it must obtain 2 electrons, and this it does by sharing the 2 lone electrons of the nitrogen atoms, and since both electrons are derived from the nitrogen, and not one each from N and H, the union is a co-ordinate link



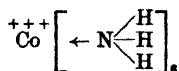
With unionized ammonium chloride the structure is



with covalent linkages only.

In all the complex cobalt, iron and chromium compounds it will be found that they can be represented as built up by means of covalent and co-ordinate linkages, and in a great many cases it is found that by the formation of these complexes the central atom, cobalt or iron, attains the stable electronic structure of the next inert gas.

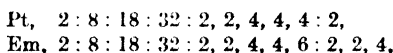
Thus the compound  $\text{Co}(\text{NH}_3)_6\text{Cl}_3$  is a salt and ionizes into  $\text{Co}^{+++}(\text{NH}_3)_6$  and  $3\text{Cl}^-$ , the co-ordination number of the complex ion is 6, and it can be represented as



The ionic structure of the Co atom is 2 : 2, 2, 4 : 2, 2, 4, 4, 4 : 1, and that of Krypton 2 : 2, 2, 4 : 2, 2, 4, 4, 6 : 2, 2, 4, i.e. the Co atom is 9 electrons short of the nearest stable arrangement, but the Co ion has already given up 3 electrons so that  $\text{Co}^{+++}$  is 12 electrons short, and these it obtains by sharing a lone pair of electrons from each molecule of  $\text{NH}_3$ .

In the case of the compound  $\overset{+}{\text{Co}}\overset{+}{\text{Cl}}\text{5NH}_3\text{2}\bar{\text{Cl}}$ , the  $\overset{+}{\text{Co}}$  is 11 electrons short, and these it obtains as follows, viz. 10 from the 5 molecules of ammonia as above and one from the chlorine atom, this latter link is a covalent one, and the Co and Cl each contributes an electron.

Somewhat similar phenomena will be found with the complex platinum compounds and the relationship of Pt to the nearest inert gas Em:



i.e. 6 electrons short in the 6th sphere and 2 in the 5th, a total of 8.

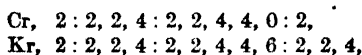
In compounds like  $\overset{+}{\text{Pt}}(\leftarrow\text{NH}_3)_6\text{4}\bar{\text{Cl}}$  and  $2\bar{\text{K}}\overset{+}{\text{Pt}}(\text{---}\text{Cl})_6$ , in both of which the co-ordination number is 6, the Pt gains  $12 - 4$ , i.e. 8, and  $6 + 2$ , i.e. 8, electrons respectively, and so has the stable configuration.

Also in the neutral non-ionized compound  $\text{Pt2NH}_3\text{2Cl}$ , which has a covalent number 4, the Pt atom gains 6 electrons—two short of the stable arrangement.

With iron compounds such as  $\text{Fe6H}_2\text{O2}\bar{\text{Cl}}$  and  $\text{FeCl}_2\text{4H}_2\text{O}$  (neutral) 10 electrons are required to transform the iron system into the stable Krypton system, and these are available in the two cases.\*

The well-known ferro- and ferricyanides, e.g.  $[\overset{+}{\text{Fe6CN}}]\overset{+}{4\bar{\text{K}}}$  and  $[\overset{+}{\text{Fe6CN}}]\overset{+}{3\bar{\text{K}}}$ , in the former of which the Fe is bivalent and in the second trivalent, are of the same type, and the form contains the stable Krypton system. In these and the corresponding Prussian blues and Berlin green the cyanide group are arranged octahedrally around the central iron atom (either ferrous or ferric) state, and the lattice structure of all the compounds has been worked out by *Keggin* and *Miles* (*Nature*, 1936, by adopting X-ray methods).

With complex chromium salts the stable arrangement is not attained. The arrangements for Cr and Krypton are:



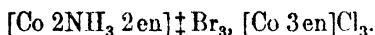
and Cr is 12 electrons short of the stable Krypton arrangement.

\* See p. 706.

The common chromium complexes are of the types  $\text{Cr}^{\text{++}\text{+}}\text{6NH}_3$ ,  $\text{3Cl}^-$ ,  $\text{Cr}^{\text{++}\text{+}}\text{5NH}_3\text{H}_2\text{O}$   $\text{3Cl}^-$ ,  $\text{Cr}^{\text{++}\text{+}}\text{2NH}_3\text{4H}_2\text{O}$  \*  $\text{3Cl}^-$ ,  $\text{Cr}^{\text{++}\text{+}}\text{Cl5NH}_3$   $\text{2Cl}^-$ ,  $\text{CrCl}_2\text{4NH}_3$   $\text{Cl}^-$ , and  $\text{CrCl}_3\text{2NH}_3\text{H}_2\text{O}$ , in all of which the chromium atom is 3 electrons short of the stable Krypton number.

Numerous organic co-ordinate compounds of cobalt, platinum, iron and chromium are known belonging to the same types as those just mentioned, but with organic bases replacing  $\text{NH}_3$ . In a few cases these contain monamines, e.g.  $\text{C}_2\text{H}_5\text{NH}_2$ , but the great majority contain diamines, the commonest of which is ethylenediamine,  $\text{NH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$ , which takes the place of 2 molecules of ammonia as each N atom can supply a lone pair of electrons; in formulæ this molecule is denoted by *en*. Such molecules become attached to the central atom at two points, and have been termed by *Morgan* **chelate** † groups, and the ring so formed a chelate

ring, Co  $\begin{array}{c} \swarrow \text{NH}_2\cdot\text{CH}_2 \\ | \\ \nwarrow \text{NH}_2\cdot\text{CH}_2 \end{array}$ . Compounds of this type are:



2 : 2'-dipyridyl,  $\text{C}_5\text{H}_4\text{N}\cdot\text{C}_5\text{H}_4\text{N}$ , is another twofold chelate group and is denoted by *dipy* as in the compounds  $[\text{Fe } 3\text{dipy}]\text{Br}_2$ ,  $6\text{H}_2\text{O}$  and  $[\text{Ni } 3\text{dipy}]\text{Cl}_2$ ,  $6\text{H}_2\text{O}$ .

Threefold groups, i.e. groups which can replace three molecules of ammonia are  $\alpha\beta\gamma$ -triaminopropane (*typ*), e.g.  $[\text{Co } 2\text{typ}]\text{Cl}_3$  and  $[\text{Rh } 2\text{typ}]\text{I}_3$  and 2 : 2' : 2''-tripyridyl (*trip*), e.g.  $[\text{Fe } 2\text{trip}]\text{Br}_2$ ,  $1\cdot5 \text{ H}_2\text{O}$  and  $[\text{Ni } 2\text{trip}]\text{Br}_2$ ,  $3\text{H}_2\text{O}$ .

A fourfold associating unity is ethylenediamine-bisacetylacetone  $[\cdot\text{CH}_2\cdot\text{N}:\text{CMe}\cdot\text{CH}:\text{CMe}\cdot\text{OH}]_2$ , termed *ec*, which forms stable complexes  $[\text{Co } 2\text{NH}_3 \text{ ec}]\text{Br}$ .

For stereochemistry of co-ordinated compounds cf. Chap. I, F.

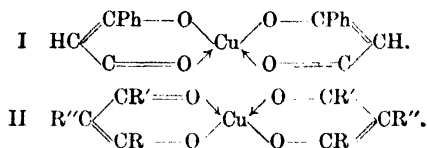
\*  $\text{H}_2\text{O}$ , i.e.  $\begin{array}{c} \text{H} \\ \diagup \text{O} \diagdown \\ \text{H} \end{array}$ , can be a donor of a lone pair of electrons in the same manner as  $\text{NH}_3$ .

† From the Greek denoting crab's pincer claw.

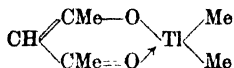
‡ The portion within the bracket is the complex cation and the atoms outside are the anions.



Copper also forms chelate rings with benzoyl-pyruvic acid I, and with  $\beta$ -diketones II:

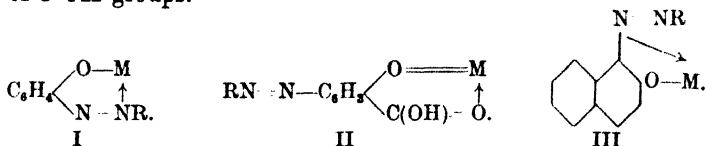


4. **Thallium.**—The compound  $\text{TlMe}_2\text{I}$  is ionic,  $\text{TlMe}_2^+ + \text{I}^-$ , but the compound formed from acetylacetone, viz.  $\text{CH}_3\text{C}(\text{OTlMe}_2):\text{CH}\cdot\text{CO}\cdot\text{CH}_3$ , is non-ionic in character, dissolves readily in benzene, has a low melting-point, and sublimes in vacuo, hence it is regarded as a chelate compound:



with 8 electrons in outer shell of Tl. Numerous homologues are known (J. C. S., 1936, 1678).

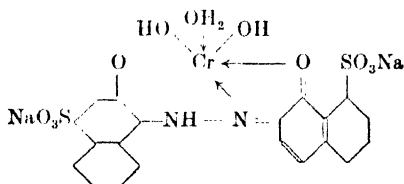
5. **Lakes.**—Most mordant dyes contain the metal of the mordant in the form of a chelate ring with the dye. Types of diazo-dyes are (1) Diazotized amines with an ortho OH (H substituted by metal) group. (M = monovalent metal.) (2) A diazotized amino-salicylic acid II. (3) The product formed from a diazonium salt and  $\beta$ -naphthol III where frequently M = Fe, Cr, Al, and in such case can replace the 3 H of 3 OH groups.



The mordant alizarin dyes contain chelate rings of much the same type.

With a trivalent metal like Cr the lake may be of the type  $\cdot\text{Cr}(\text{OH})_2$  attached to the O of the OH of the dye or  $:\text{Cr}$  attached to 3 oxygens of 3 distinct OH groups. In addition the Cr will be co-ordinated with other O or N atoms and sometimes with  $\text{OH}_2$ , and the Cr electron system will usually be of the type

mentioned on p. 706, viz. 3 short of the Krypton system, e.g. Palatine fast-blue, G.G.N.

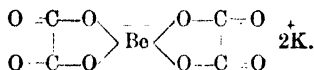


6. The beryllium compounds of acetylacetone and similar diketones are true chelate compounds:



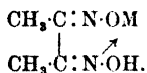
and also the similar Al compounds with 3 chelate rings.

Potassium oxalate-beryllium,  $K_2Be(C_2O_4)_2$ , has not a true chelate ring structure, as shown in the formula



The compound is stable and ionized; the Be atom attains the stable electron octet by sharing 4 electrons with 4O atoms and by taking two from the two K atoms.

7. Metallic derivatives of  $\alpha$ -dioximes are chelate, e.g. the Ni compound of dimethylglyoxime:



All chelate rings differ from holo- or heterocyclic compounds by the presence of co-ordinate links, and hence are less stable. In nearly all cases they form six-membered rings.

Carboxylic acids and their salts are not usually represented by the chelate rings:



and such four-membered chelate rings are not known.



## C. Chelate Rings involving Hydrogen

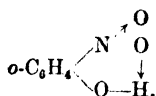
## The Hydrogen Bridge \*

Compounds of Class A containing the groups  $\begin{array}{c} \text{O} \\ \diagup \text{C} \\ \diagdown \text{OH} \end{array}$ ,  $:\text{N}\cdot\text{OH}$ ,

$\text{R}\cdot\text{OH}$  show considerable association (polymerization) in benzene, whereas the corresponding alkyl compounds (Class B)

$\begin{array}{c} \text{O} \\ \diagup \text{C} \\ \diagdown \text{OR} \end{array}$ ,  $:\text{N}\cdot\text{OR}$ ,  $\text{R}\cdot\text{O}\cdot\text{R}'$  do not. Further, compounds of

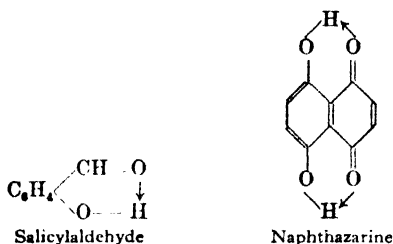
group A do not tend to associate in water or acetic acid, as they form compounds with this solvent rather than with themselves. A comparison of *o*-, *m*-, and *p*-hydroxy-aromatic compounds, e.g. nitrophenols, shows that the *m*- and *p*-compounds exhibit the characteristic association in benzene, whereas the ortho-compounds do not. This is usually attributed to internal association or chelation



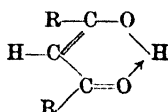
and the same holds good for hydroxy-benzaldehydes, hydroxy-benzoic esters (OH and O of  $\text{CO}_2\text{Et}$ ) in naphthalene solution, also with compounds  $\text{o-X}\cdot\text{C}_6\text{H}_4\cdot\text{NHAc}$ , where  $\text{X} = \text{NO}_2$  or  $\text{CHO}$ . As a rule a six-membered ring is formed. Thus  $\text{o-NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{NHAc}$  is chelated (6 ring), but  $\text{o-NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{NHAc}$  is not (7 ring). Similarly,  $\text{o-CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{NHAc}$  is not appreciably associated as it involves a 5 ring. Further arguments in support of the chelation of such *o*-compounds are the facts that they are less soluble in water than their isomerides, they show less tendency to form co-ordination compounds with water, and their infra-red spectra do not exhibit the absorption bands characteristic of true hydroxy-compounds. When 2OH are ortho or peri to CO, then double

\* Lassettre, *Chem. Rev.*, 1937, 259; Huggins, *J. Org.*, 1936, 409.

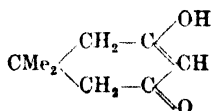
chelation can occur, e.g. naphthazarine (5:8-dihydroxy-*a*-naphthaquinone).



Similarly, acetylacetone, benzoylacetone and dibenzoylmethane appear to be free from hydroxyl groups, and hence are chelated:



The compound



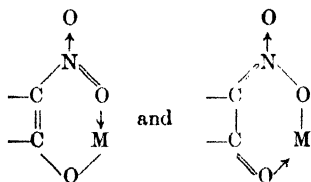
shows the presence of free hydroxyl groups and the formation of a six-membered chelate ring is difficult from stereochemical considerations.

Chelation does not always occur, thus saturated ethylene glycols, amino-alcohols and diamines which theoretically could give five-membered chelate rings involving a hydrogen bridge do not appear to do so; similarly, *o*-dihydroxy-benzene or 1:3-glycols do not chelate although six-membered rings would be formed.

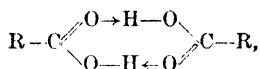
The hydrogen bridge can be represented as formed by singlet links (p. 21) between H and O.

The usual chelate rings contain two conjugated covalent links as in *o*-substituted phenols,  $\beta$ -diketones, and  $\beta$ -ketonic esters. As a rule when H is replaced by metal the chelate compounds are more stable, and there is the possibility

of resonance (Chap. LXXIII), e.g. ortho-nitro-phenol salt.



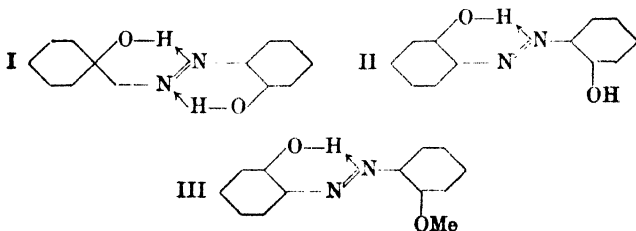
The association (polymerization) met with in carboxylic acid, alcohols, &c., is probably due to intermolecular chelation, two molecules being involved:



and an eight-membered ring being formed. This is a fairly stable ring, as the angle of 2 covalent hydrogen is  $180^\circ$ .

For further examples of chelate rings cf. chlorophyll.

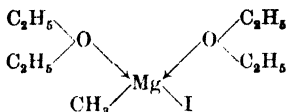
*o*-Dihydroxyazo-benzene,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{N}\cdot\text{C}_6\text{H}_4\cdot\text{OH}$ , appears to have structure I in  $\text{CCl}_4$  but structure II in ether, as in the latter solvent the physical properties are similar to those of the methyl ether III



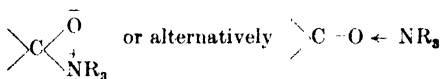
## D. Organic Molecular Compounds

Many of the molecular or additive compounds formed by organic molecules referred to in previous chapters are now regarded as co-ordinate complexes. Some of the commoner of these are:

(1) The relatively stable compounds of *Grignard* compounds with ether.

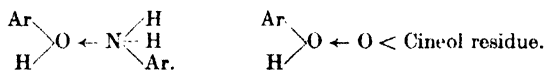


(2) Additive compounds of quinones with amines; the  $>\text{C}=\text{O}$  becomes  $>\text{C}=\ddot{\text{O}}$ , and this with  $\text{NR}_3$ , the N acting as donor, forms



(cf. *Bennett and Willis*, J. C. S., 1929, 262).

(3) Additive compounds of phenols with arylamines and with cineol (p. 972) (*Philip*, J. C. S., 1903, 829; *Morgan and Pellet*, J. S. C. I., 1935, 22T).



(4) Additive compounds of trinitrobenzene with arylamines, &c. (cf. p. 422), and also with phenolic ethers and hydrocarbons can be represented as follows:

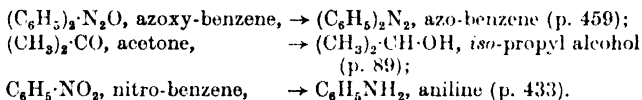
One of the nitro-groups  $-\text{N} \begin{array}{c} \text{O} \\ \diagup \text{O} \diagdown \end{array} + \text{NR}_3$  gives  $-\text{N} \begin{array}{c} \text{O} \\ \diagup \text{O} \diagdown \\ \text{NR}_3 \end{array}$ , the N

of the nitro-groups being the acceptor. With aromatic hydrocarbon one olefine link may become polarized,  $-\text{CH}=\text{CH}-$  becomes  $-\text{CH}=\text{CH}^+-$ , which adds on to the N of the nitro-group.

(*Baker and Bennett*, Rep., 1931, 134; cf. also *Hammick and Sixsmith*, J. C. S., 1935, 583, and discussion C. and I., 1938, 512; *Bernal*, Trans. Far., 1936, 211.)

## XLVII. REDUCTION

**Reduction** is the name usually given to a reaction in which oxygen is withdrawn from, or hydrogen added to, a compound; in certain cases both of these processes occur. Numerous cases of reduction have been mentioned in the preceding chapters, as examples:



As the reaction is so general, a more detailed discussion of it is given in this chapter.

In addition to the above reactions, viz. withdrawal of oxygen or addition of hydrogen, the process previously referred to as inverse substitution (p. 32)—the replacement of halogen by hydrogen, e.g.  $\text{C}_2\text{H}_5\text{I} \rightarrow \text{C}_2\text{H}_6$ —is usually regarded as a type of reduction.

The processes of reduction and oxidation occur at the same time, as the substance reduced (e.g. dichromate or nitric acid) supplies oxygen to bring about the oxidation of a carbon compound.

In terms of electron changes, when an atom or ion is reduced it gains electrons, and conversely when an atom or ion is oxidized it loses electrons. A reducing agent is therefore one which is capable of donating electrons.

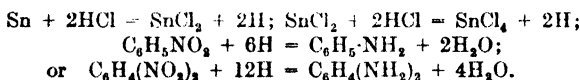
A. "**Nascent Hydrogen**".—Of the numerous methods that can be employed for reduction, one of the commonest is by means of "nascent hydrogen", i.e. hydrogen generated in the presence of the substance to be reduced. The fact that the majority of these reductions cannot be effected by means of ordinary gaseous hydrogen, but can be readily attained by the use of hydrogen at its moment of formation, is used as an argument in favour of the view that nascent hydrogen consists of the free atoms. Reductions by this method can be conducted under very varying conditions; and it is of extreme importance to note that the conditions are a prime factor in determining the nature of the product. It has already been pointed out that the reduction of nitro-benzene can give rise

to azoxy-benzene, azo-benzene, phenyl-hydroxyl-amine, or aniline, according to the conditions under which the reaction occurs; and similar phenomena have been mentioned in the case of the reduction of terephthalic acid (Chap. XXVI, B.).

Such reductions may take place in acid, alkaline, or neutral solution, and this affords a simple method of classification for these reactions.

(a) **Reduction in Acid Solution.**—Almost any combination of acid and metal which gives rise to hydrogen may be employed for this purpose; but the usual combinations are tin and hydrochloric acid, zinc and hydrochloric acid, zinc and acetic acid, zinc dust and acetic acid, iron and acetic acid.

The usual method employed in the laboratory for the reduction of nitro-compounds to the corresponding amino-compounds (see Aniline) is by means of tin and hydrochloric acid. The metal is first converted into stannous, and then into stannic chloride:



The method has certain objectionable features which render it unsuitable for use on the manufacturing scale. Among these may be mentioned (a) need for large excess of concentrated acid, and the fact that this acid will subsequently have to be neutralized. (b) The strong acid is liable to react with the reduction product, yielding halogenated amines. The introduction of the halogen into the benzene nucleus probably occurs in the following manner:



(*Bamberger*). Such chlorinated amines are always liable to be formed when concentrated hydrochloric acid is used in combination with a metal for the reduction of nitro-compounds, and in some cases, e.g. *p*-nitrophenetole, a 90 per cent yield of a chloro-compound,  $\text{NH}_2\cdot\text{C}_6\text{H}_3\text{Cl}\cdot\text{OEt}$ , is formed. By using dilute acid the formation of the chloro-compound is eliminated. (c) The reduced compound often combines with the stannic chloride to form a double salt, e.g.  $\text{C}_6\text{H}_5\text{NH}_2$ ,  $\text{HCl}$ ,  $\text{SnCl}_4$ , and certain of these are somewhat difficult to decompose.

Aliphatic nitro-derivatives may also be reduced to amines by this method, except in cases where two nitro-groups are

attached to the same carbon atom, when a ketone is formed. Other examples are the conversion of cyclic derivatives into hydro-derivatives, e.g. *p*-hydroxy-quinoline to tetrahydro-*p*-hydroxy-quinoline, and of sulphonic chlorides,  $R\cdot SO_2\cdot Cl$ , into thio-phenols,  $R\cdot SH$ .

In many cases tin-foil is stated to be preferable to granulated tin, as it exposes a larger surface, and occasionally alcoholic solutions of the hydrogen chloride are used in place of aqueous. Stannous chloride and hydrochloric acid occasionally give better yields than tin and acid; thus nitro-methane is reduced to methyl-hydroxylamine, and the method has been recommended for the estimation of nitro-groups. An excess of standard stannous chloride solution is used, and the excess titrated after the reduction is complete, each nitro-group requiring 3 gm. molecules of stannous chloride. Secondary aliphatic nitro-compounds when reduced by this method yield ketones. The isonitro-group  $\cdot NO\cdot OH$  is reduced to the oxime group  $:N\cdot OH$ , and this is hydrolysed by the acid and the ketone formed (*v. Braun*, B., 1911, 2533; 1912, 394).

Stannous chloride is sometimes used without the addition of free acid; thus *Witt*, by reducing amino-azo-benzene with alcoholic stannous chloride, obtained aniline and *p*-phenylenediamine:

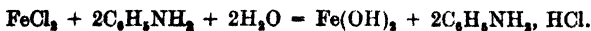


but chlorinations can also occur.

Most of the objections referred to in connexion with the reduction of nitro-derivatives by means of tin and hydrochloric acid may be avoided by using iron and acetic acid or dilute hydrochloric acid. This method is usually adopted on the manufacturing scale, as only a small amount of acid, some one-fortieth of that indicated by the equation,



is required. The reason for this may be that the ferrous chloride reacts with the aniline and water, yielding ferrous hydroxide and aniline hydrochloride:



The hydrochloride then reacts with more iron, producing

ferrous chloride and hydrogen, which can reduce more of the nitro-compound (cf. p. 433):

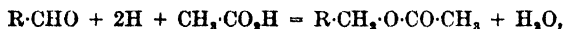
The iron method possesses further advantages, as the reduction can be regulated much more readily than in the case of tin and acid. Thus *p*-nitro-acetanilide reduced by the iron method gives the corresponding amino-compound,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ , whereas with tin and hydrochloric acid hydrolysis and reduction both occur, and the product is *p*-phenylene-diamine.

Iron and acid may also be employed for the reduction of aromatic polynitro-compounds to amino-nitro-derivatives:



but such a reduction is almost impossible with tin and acid.

Zinc, as granulated zinc, or more frequently as zinc dust, is also used in conjunction with acids, usually hydrochloric or acetic. When concentrated hydrochloric is employed, chlorine is apt to enter the benzene ring (cf. p. 715); with glacial acetic acid (*Krafft*s, B., 1883, 1715) acetyl derivatives are formed occasionally instead of the simple reduction products. For example, when aldehydes are reduced, alkyl acetates and not alcohols are formed:



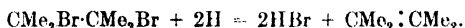
and when nitro-derivatives are reduced, acetylated amines are obtained. Although aliphatic ketones cannot be reduced by this method, all ketones containing one or two benzene nuclei directly attached to the carbonyl group are readily reduced to pinacones (p. 222). Hydroxy-derivatives of anthraquinone may also be reduced in a similar manner, one or more of the hydroxy-groups being replaced by hydrogen, and aliphatic nitro-derivatives, such as nitro-guanidine,  $\text{NH}:\text{C}(\text{NH}_2)\cdot\text{NH}\cdot\text{NO}_2$ , may be reduced to the corresponding amino-compounds; the method is also used for the reduction of higher alkyl halides to hydrocarbons (*Clarke*, J. A. C. S., 1908, 1147; 1909, 113).

Hydrochloric acid and amalgamated zinc reduce ketones of the type of acetophenone to the corresponding hydrocarbons, and the reaction is of special interest for the preparation of certain substituted phenols, e.g. *p*-ethylphenol,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_3$ , from *p*-hydroxy-acetophenone (B., 1913, 1837; 1914, 51).

A transformation occasionally effected by means of zinc dust

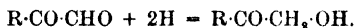


and glacial acetic acid is the removal of two atoms of halogen and the conversion of a saturated compound into an olefine, e.g. tetramethyl-ethylene dibromide into tetramethyl-ethylene.

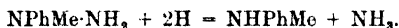


All peroxides (p. 209) are readily reduced by this method, e.g. diethyl-peroxide,  $\text{Et}_2\text{O}_2$ , to ethyl alcohol (or ethyl acetate).

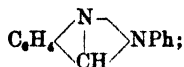
Dilute acetic acid is frequently used with zinc dust. This is the usual method adopted for the reduction of osones to ketoses (*Fischer*) (p. 343):



It is also extremely useful in the preparation of hydrazines from nitrosamines and nitramines, e.g. *Fischer* (A., 1886, **236**, 198) obtained methyl-phenyl-hydrazine,  $\text{NPhMe}\cdot\text{NH}_2$ , by the reduction of methyl-phenyl-nitrosamine,  $\text{NPhMe}\cdot\text{NO}$ . Other reducing agents, e.g. metal and concentrated hydrochloric acid, stannous chloride, zinc dust and alkali, are all liable to carry the reduction a stage further and yield a mixture of ammonia and amine:



An extremely interesting example of the influence of the reducing agent and the method of reduction on the nature of the final product is met with in the case of *o*-nitro-benzyl-phenyl-nitrosamine,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{NPh}\cdot\text{NO}$ . With tin and hydrochloric acid it yields phenyl-indazole,

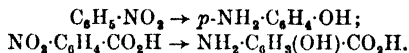


with sodium amalgam, in alkaline solution, *o*-amino-benzyl-aniline,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{NHPh}$ , and ammonia; and with zinc dust and glacial acetic acid, *o*-amino-benzyl-phenyl-hydrazine,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{NPh}\cdot\text{NH}_2$  (*Busch*, B., 1894, 2899).

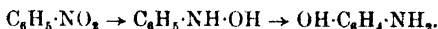
With zinc dust and dilute sulphuric acid the reaction is somewhat slower than with acetic acid; with these reagents sulphonic chlorides may be transformed into thio-phenols, or the reaction may proceed a stage further and the sulphur be completely removed.

Zinc dust and concentrated sulphuric acid are occasionally used for the reduction of nitro-compounds, and in all cases the

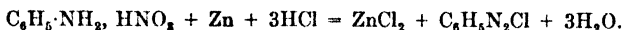
product is an amino-hydroxy- and not a simple amino-derivative:



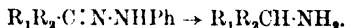
Probably a phenyl-hydroxylamine is first formed, and this then yields the amino-phenol (cf. p. 460):



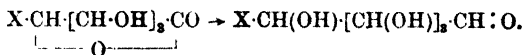
When zinc or zinc dust and any acid are added to the nitrate of an aromatic amine, a diazonium salt is formed:



Sodium amalgam is sometimes used as a reducing agent in the presence of acid: thus with acetic acid it is used for the reduction of hydrazones to primary amines:



Reductions by means of sodium amalgam and dilute sulphuric acid have been largely used by *E. Fischer* in his synthetical work on the sugars, since the lactones of hydroxy acids when reduced in this way at 0° yield aldoses (p. 343):



A very common acid-reducing agent is hydriodic acid, its reducing action being attributed to the decomposition of the hydrogen iodide into iodine and nascent hydrogen at moderate temperatures. The method was first introduced by *Berthelot*, who, in his earlier experiments, used the acid alone; but when he found that the liberated iodine interfered with the reduction by giving rise to iodo-derivatives or by oxidizing, he added red phosphorus or sometimes phosphonium iodide. The function of the phosphorus is to combine with the iodine immediately it is liberated from the hydrogen iodide, and thus form phosphorus tri-iodide, which is then decomposed by the water present, yielding hydrogen iodide and phosphorous acid. Phosphonium iodide is often formed as a by-product in these reductions. With hydriodic acid alone, practically all oxygen compounds are reduced to saturated hydrocarbons at a temperature of 275°, the reduction being conducted in

sealed tubes, e.g. glycerol yields propane. Amines are also transformed into paraffins, e.g. methylamine yields methane.

When hydriodic acid and phosphorus are used, the reduction can either take place in open vessels, e.g. a flask with reflux condenser, or in sealed tubes if a higher temperature is required. As examples of the former we have the following:  $\text{CHI}_3 \rightarrow \text{CH}_2\text{I}_2$ ; anthraquinone  $\rightarrow$  dihydro-anthracene; benzoic acid,  $\text{OH}\cdot\text{C}_6\text{H}_5\cdot\text{CO}_2\text{H} \rightarrow$  diphenyl-acetic acid,  $\text{CHPh}_2\cdot\text{CO}_2\text{H}$ ; trihydroxy-glutaric acid,  $\text{CO}_2\text{H}\cdot[\text{CH}\cdot\text{OH}]_3\cdot\text{CO}_2\text{H} \rightarrow$  glutaric acid; mixed ketones, e.g.  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3 \rightarrow$  hydrocarbons.

As examples of the latter we have the conversion of fatty acids, from  $\text{C}_8\text{H}_{17}\cdot\text{CO}_2\text{H}$  upwards into paraffin-hydrocarbons, the reduction of anthracene to hydro-anthracenes, and of hydroxy-cyclohexane-carboxylic acid,  $\text{OH}\cdot\text{C}_6\text{H}_{10}\cdot\text{CO}_2\text{H}$ , to hexahydro-benzoic acid,  $\text{C}_6\text{H}_{11}\cdot\text{CO}_2\text{H}$ .

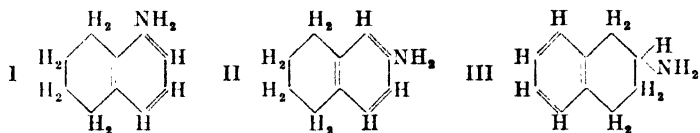
Hydriodic acid is not a good reducing agent for nitro-compounds; as a rule it leaves the nitro-group intact, e.g. nitro-benzene-sulphonic chloride,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\text{Cl}$ , yields first  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{SO}\cdot\text{SO}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2$ , and ultimately *m*-dinitro-diphenyl-disulphide,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{S}\cdot\text{S}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2$ .

Concentrated sulphuric acid and aluminium form a convenient reagent for reducing the CO groups in benzophenone and anthraquinone to CH·OH groups (M., 1917, 11).

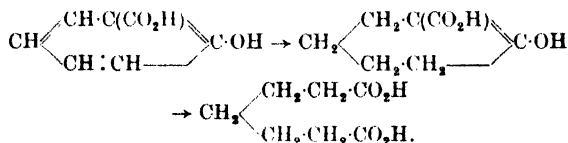
(b) **Nascent Hydrogen in Alkaline Solution.**—One of the commonest methods is the addition of metallic sodium, in the form of wire or thin strips, to boiling ethyl alcohol; as a rule it is necessary to use absolute alcohol, as the presence of water diminishes the yields. As examples, we have the reduction of nitriles to primary amines,  $\text{R}\cdot\text{CN} \rightarrow \text{R}\cdot\text{CH}_2\cdot\text{NH}_2$  (p. 117), of esters to alcohols (p. 79), of naphthalene to dihydro-naphthalene, of pyridine to piperidine (p. 685), although quinoline is not so readily converted by this process into tetrahydro-quinoline, and lastly, of various benzene derivatives, e.g. *m*-hydroxy-benzoic acids into corresponding hexahydro-derivatives, i.e. derivatives of cyclohexane. When a higher temperature is required than can be attained with ethyl alcohol, boiling amyl alcohol is used (*Bamberger*). By this method naphthalene and its derivatives may be converted into their tetrahydro-compounds, e.g. the naphthols,  $\text{C}_{10}\text{H}_7\cdot\text{OH}$ , into tetrahydro-naphthols,  $\text{C}_{10}\text{H}_{11}\cdot\text{OH}$ .

It is interesting to note that the chief reduction product obtained from *a*-naphthylamine is *ar*-tetrahydro-*a*-naphthyl-

amine (I), and from  $\beta$ -naphthylamine a mixture of *ar*- and *ac*-tetrahydro-derivatives (II and III):



Similarly phenanthrene is reduced to its tetrahydro-derivative, anthracene to its dihydro-compound, and the benzene carboxylic acids to di-, tetra-, or hexahydro-derivatives, according to the temperature and other conditions of reduction (cf. p. 537); with sodium and boiling amyl alcohol, benzoic acid yields mainly  $C_8H_{11}\cdot CO_2H$ . In a few cases, when substituted benzoic acids are reduced by this method, a rupture of the ring occurs and an aliphatic acid is formed. One of the best-known examples is the reduction of salicylic acid to pimelic acid (p. 404); in this case it may be assumed that a tetra-hydro-salicylic acid is first formed, and that by the addition of the elements of water this is converted into pimelic acid:



Although aniline cannot be converted into its hydro-derivatives by this method, aniline-*o*-sulphonic acid yields a hexahydro-derivative. In place of alcohol moist ether is sometimes used in conjunction with sodium. This is generally accomplished by adding the metal to ether floating on water, or better, on a solution of sodium bicarbonate. Dibenzyl ketone can thus be reduced to dibenzyl-carbinol, mesityl oxide to methyl-isobutyl-carbinol, and acid chlorides,  $R\cdot COCl$ , to the corresponding alcohols,  $R\cdot CH_2\cdot OH$ .

Sodium amalgam may be used in place of sodium itself, as a rule in combination with water; the amalgam is added gradually and the mixture kept agitated, and a small amount of alcohol is added, if necessary, to prevent frothing. By this method, benzene and its derivatives may be reduced to di- and tetrahydro-compounds. Many olefine derivatives are reduced

to saturated compounds, e.g. cinnamic acid,  $C_6H_5 \cdot CH:CH \cdot CO_2H$ , to phenyl-propionic acid,  $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CO_2H$ , and ketones to secondary alcohols. Alcohol is occasionally a better medium than water, and by this method azo- may be reduced to hydrazo-compounds (Chap. XXII, C2), and benzaldehyde and its substituted derivatives to benzyl alcohols.

In many instances the alkali formed by the action of the metal on water or alcohol has a deleterious action on the products of reduction, and it becomes necessary to neutralize the alkali as far as possible. This may be effected by the occasional addition of mineral acid, but is most readily accomplished by *Aschan's* method of leading carbon dioxide through the liquid as the reduction proceeds, and in this way converting the sodium hydroxide into bicarbonate as fast as formed. It is the method often used in the reduction of phthalic acids, &c., and may also be employed for converting naphthalene and resorcinol into their dihydro-derivatives, and benzoic acid into its tetrahydro-compound.

Zinc and alkali are often used to reduce aromatic ketones to secondary alcohols, e.g.  $(C_6H_5)_2CO \rightarrow (C_6H_5)_2CH \cdot OH$ ; whereas when zinc and acetic acid are used, the corresponding pinacones,  $(C_6H_5)_2C(OH) \cdot C(OH)(C_6H_5)_2$ , are formed. Alkali, especially sodium hydroxide, may be used with zinc dust; the usual method being to keep the alkali and substance well stirred, and to add the zinc dust gradually. As examples we have: Anthraquinone  $\rightarrow$  anthranol; fatty diazo-compounds  $\rightarrow$  hydrazo-compounds; *o*-nitraniline  $\rightarrow$  *o*-phenylenediamine. Further examples are the dehalogenating of aromatic compounds and the preparation of azoxy- and azo-compounds (Chap. XXII, C1).

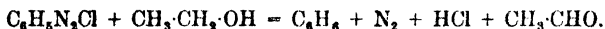
(c) **Nascent Hydrogen in Neutral Solution.**—Many reductions take place most readily in the absence of free acid or free alkali, and may be effected by the following reagents: (i) Zinc filings or granulated zinc and alcohol, e.g.  $\beta$ -bromo-allo-cinnamic acid  $\rightarrow$  allo-cinnamic acid (Chap. XXVI, A2); (ii) *Gladstone-Tribe* couple, in the reduction of alkyl halides to paraffins (p. 32; J. C. S., 1913, 1292); (iii) Zinc dust and saturated ammonium chloride for reducing nitro-ketones and nitro-acyl-derivatives; (iv) mixture of zinc and iron, in the presence of certain metallic salts, e.g. acetone  $\rightarrow$  isopropyl alcohol; (v) zinc dust and water (or alcohol), which may be used for reducing azo-dyes to mixtures of amines, e.g. chrysoidine,  $NPh:N \cdot C_6H_3(NH_2)_2$ , to aniline

and triamino-benzene, and also for reducing aromatic nitro-compounds to the corresponding hydroxylamines, e.g.  $C_6H_5 \cdot NO_2 \rightarrow C_6H_5 \cdot NH \cdot OH$ , a reaction which proceeds extremely readily in the presence of ammonium chloride solution. The same reagents are extremely useful in converting sulphonic chlorides into sulphinic acids,  $C_6H_5 \cdot SO_2Cl \rightarrow C_6H_5 \cdot SO_2H$ . (vi) Aluminium amalgam (*Cohen and Ormandy*, B. A., Report, 1889, 550) is also a useful neutral reducing agent in the presence of water; by this method nitro-derivatives are readily transformed into hydroxylamines, and ketones to secondary alcohols.

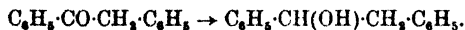
Benzophenone reduced in acid solution gives benzopinacol,  $OH \cdot CPh_2 \cdot CPh_2 \cdot OH$ , in alkaline solution benzhydrol,  $CPh_2 \cdot CH \cdot OH$ , and in neutral aqueous solution with aluminium amalgam and alcohol, a mixture of 66 per cent of the latter and 33 of the former.

B. Among other chemical methods may be mentioned **heating with metals**. Thus azo-benzene is formed when azoxy-benzene is heated with metallic iron, anthracene when alizarin is heated with zinc dust, and pyrrole when succinimide is heated with the same reagent. In all these cases the metal abstracts oxygen and is converted into an oxide. It is a method frequently adopted when dealing with unknown complex substances and it is desired to know from what simpler compounds they are derived.

**Alcohol alone**, as in the conversion of diazonium salts into hydrocarbons (Chap. XXII, A.):



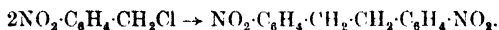
**Sodium ethoxide**, or often alcoholic potash, for the reduction of nitro-compounds to azoxy- or azo-compounds (*De Bruyn*), and also for reduction of deoxy-benzoin and other aromatic ketones to secondary alcohols, e.g. hydroxy-dibenzyl:



The **alkoxides of aluminium and magnesium**  $Al(OR)_3$ ,  $Mg(OR)_2$ , are useful reducing agents for obtaining alcohols from aldehydes, ketones or methoxyaromatic aldehydes (*Merwein*, J. pr., 1936, ii, 147, 211), and the *alkyl* derivatives of aluminium or boron, e.g.  $AlEt_3$ , can be used for similar purposes (*ibid.* 226).

**Sodium stannite**, obtained by adding an excess of sodium

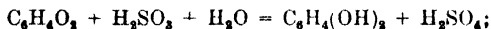
hydroxide to stannous chloride, is employed for preparing azo-compounds from nitrated hydrocarbons, for the reduction of diazonium salts to hydrocarbons, e.g. benzene from benzene diazonium chloride. It reduces *p*-nitro-benzyl chloride to dinitro-dibenzyl, the nitro-groups remaining intact:



**Hydrogen sulphide**, or **ammonium sulphide**, in alcoholic solution (*Cohen and M'Candlish*, J. C. S., 1905, 1257, or pyridine, 1929, 2264), is made use of for the reduction of nitro- and nitroso-derivatives to amines, and is especially useful when several nitro-groups are present and it is required to reduce only one, e.g.  $m\text{-C}_6\text{H}_4(\text{NO}_2)_2 \rightarrow m\text{-NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$ ,  $\text{C}_6\text{H}_2\text{Me}(\text{NO}_2)_3 \rightarrow \text{NH}_2\cdot\text{C}_6\text{H}_2\text{Me}(\text{NO}_2)_2$ , &c.; also *o*-nitro-cinnamic acid  $\rightarrow \alpha$ -hydroxy-quinoline or carbostyryl (p. 692). In many cases sulphur-derivatives are formed instead of simpler reduction products, especially with ketones or aldehydes.

Sometimes a nitro-group is removed, e.g.  $(\text{NO}_2)_2\text{C}_6\text{H}_3\text{Me}$  yields  $[\text{NO}_2\cdot\text{C}_6\text{H}_3\text{Me}]_2\text{S}$ .

**Sulphurous acid** is used in reducing quinones to quinols, e.g.



and **sodium hyposulphite**,  $\text{Na}_2\text{S}_2\text{O}_4$ , is an extremely useful reagent for preparing leuco-compounds from dyes.

**Ferrous sulphate** and **ammonia** form a convenient reducing agent for certain nitro-compounds, e.g. nitro-phenylacetic acid, nitro-benzaldehyde and nitro-cinnamic acid.

**Phenylhydrazine** is a useful agent for reducing  $\delta$ -trinitro-tri-aminobenzene to hexaminobenzene (J. C. S., 1929, 334).

C. **Catalytic Reduction**, or **Catalytic Hydrogenation**; cf. Chap. LXIX, A.

D. **Electrolytic Reduction**.\*-- This reduction is effected by the cathodic hydrogen produced by the electrolysis of aqueous solutions of acids or alkalis. The actual products formed are dependent not merely on the substances reduced, but also upon the conditions: (a) nature and concentration of solvent; (b) strength of current or the current density; (c) the materials of which the electrodes are made, due to the difference of potential at which the hydrogen ions are discharged (as a

\* *Electrolytic Oxidation and Reduction*, Glasson and Hickling, London, 1928.

# NITRO-BENZENE IN THE CATHODE COMPARTMENT

Cathode compartment	Anode compartment	Electrodes	Current density in amperes	Voltage	Temperature	Time in ampere hours	Product
Alcohol + twice its weight of 25-per-cent sulphuric acid	25-per-cent sulphuric acid	Lead	4-5	3-7-4	65°-80°	35	Aniline and <i>p</i> -amino-phenol
Concentrated sulphuric acid + little water	Concentrated sulphuric in porous cell	Platinum	5-6	7-8	75°-80°		<i>p</i> -Amino-phenol
3-per-cent sodium hydroxide	15-per-cent sodium sulphate with very little sulphuric acid	Anode lead Cathode nickel	5-6	6-8		22	Azoxy-benzene
70-per-cent ethyl alcohol with sodium acetate	Cold saturated sodium carbonate solution in porous cell	Anode platinum Cathode nickel	6-8	8-9		30	Azo-benzene
70-per-cent ethyl alcohol with sodium acetate	Cold saturated sodium carbonate solution in porous cell	Anode platinum Cathode nickel	First 6-8 then 2-3	8-9		35	Hydrazo-benzene
Concentrated hydrochloric acid	20-per-cent sulphuric acid	Platinum	1-5-2	5-6-5		50	<i>o</i> - and <i>p</i> -chlor-anilines

The yield of *p*-amino-phenol can be increased by using a copper cathode and lead in the electrolyte

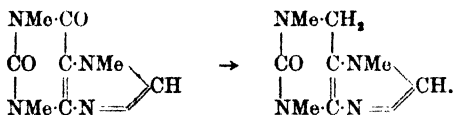


rule platinum, mercury, or lead electrodes are used); and (d) the temperature.

In many cases the reduction is carried out in a double cell provided with a diaphragm. (a) The cathode solution is placed in an ordinary unglazed porous cell, and this is introduced into a beaker which serves as the anode compartment; or (b) two glazed pots with small perforations are used, and the small annular space between these is packed with asbestos paper. If necessary the liquid can be agitated by using a rotating cathode.

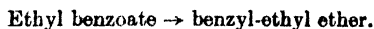
The reduction of nitro-benzene may be cited as one of the best examples which show the effect of conditions on the nature of the product (see table on p. 725).

In the reduction of ketonic compounds, *Tafel* (B., 1900, 2209) has shown that the best effects are obtained by using *pure* lead electrodes, as the hydrogen ions are thus discharged at a higher potential than when other metals are employed, and by employing in the cathode compartment 30–60 per cent sulphuric acid; with stronger acid, reduction of the acid occurs and sulphur is deposited. It is also essential that the current density shall be as low as possible (For preparation of cells see *Tafel*.) Acetone when reduced under such conditions, using mercury as cathode, yields isopropyl alcohol; but under similar conditions with a lead cathode it yields a mixture of isopropyl alcohol and pinacone. Camphor may be reduced to borneol (Chap. LVII, C2), and caffeine to deoxy-caffeine:



Further, acetanilide,  $\text{C}_6\text{H}_5 \cdot \text{NH} \cdot \text{CO} \cdot \text{CH}_3$ , may be reduced to ethyl-aniline,  $\text{C}_6\text{H}_5 \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{CH}_3$ ; pyridine to piperidine, using lead cathodes; aconitic acid to tricarballic acid and cinnamic to hydrocinnamic acid, by using mercury cathodes.

The esters of oxalic, malonic, acetoacetic, benzoic, and phthalic acids, when reduced electrolytically, yield ethers, e.g.:



**E. Reduction by Micro-organisms.**—Yeast, either in the

presence or absence of sugar, can convert acetaldol,  $\text{OH}\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CHO}$ , into  $\beta$ -tutylene glycol,  $\text{OH}\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , acetaldehyde to alcohol, and citral into geraniol (*Neuberg*, 1918).

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## XLVIII. OXIDATION

**Oxidation** includes not only those processes in which oxygen is added to a compound, e.g. conversion of an aldehyde,  $\text{R}\cdot\text{CH}:\text{O}$ , into an acid,  $\text{R}\cdot\text{CO}\cdot\text{OH}$ , but also processes in which hydrogen is withdrawn from a compound, e.g. transformation of a primary alcohol,  $\text{R}\cdot\text{CH}_2\cdot\text{OH}$ , into an aldehyde,  $\text{R}\cdot\text{CH}:\text{O}$ . In certain cases both processes can occur, e.g. oxidation of aniline,  $\text{C}_6\text{H}_5\text{NH}_2$ , to nitroso-benzene,  $\text{C}_6\text{H}_5\cdot\text{NO}$ .

In the *Cannizzaro* reaction of aromatic aldehydes with alkali 50 per cent is oxidized to the acid and 50 per cent reduced to the alcohol (Chap. XXV, A.).

Most of the oxidizing agents employed are substances rich in oxygen, e.g. potassium dichromate or permanganate, nitric acid, chromic anhydride, peroxides, &c. During the oxidation, although the organic compound is oxidized, the oxidizing substance is reduced (cf. p. 714).

The withdrawal of hydrogen from a compound is usually termed **dehydrogenation** as contrasted with hydrogenation, the addition of hydrogen.

The methods used for dehydrogenation are grouped together in Chap. XLIX, although they are not all catalytic processes, e.g. removal of hydrogen by means of sulphur or selenium.

Oxygen itself is sometimes made use of as an oxidizing agent, but usually in the presence of a catalyser, e.g. finely-divided metals such as platinum black or one of the enzymes known as oxydases. Processes of oxidation, like those of reduction, depend not merely upon the substances to be oxidized, but also on the oxidizing agent selected, and on such conditions as the acid, alkaline, or neutral nature of the solvent, temperature, and concentration. Examples of this have previously been cited among the aromatic hydrocarbons. Thus *m*-xylene is not acted upon by dilute nitric acid, but

with chromic anhydride yields isophthalic acid. A very good example is aniline:

Aniline with	Manganese dioxide and sulphuric acid	→ ammonia and little quinone;
	Dichromate mixture	→ quinone;
	Alkaline permanganate	→ azo-benzene and ammonia;
	Acidified permanganate	→ aniline black;
	Neutral permanganate	→ nitro-benzene and azo-benzene;
	Bleaching-powder	→ nitro-benzene;
	Hypochlorous acid	→ <i>p</i> -amino-phenol.

Compounds of similar constitution are not always oxidized in the same manner, thus to oxidize *p*-nitro-toluene or *p*-nitro-cinnamic acid the best reagent is dichromate mixture, but for the isomeric *o*-compounds, dilute nitric acid or permanganate are recommended. The inhibiting influence of halogen and other negative radicals in the *o*-position with regard to the alkyl group, on the oxidation of such hydrocarbons by means of acid oxidizing agents, has already been referred to (p. 507), and also the fact that the final product of oxidation of a benzene homologue depends on the number and positions of the side chains, and not on their length, each yielding ultimately a  $\text{CO}_2\text{H}$  group.

When a compound like cymene,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{C}_3\text{H}_7$ , is selectively oxidized, it is usually the longer side chain which is first affected; and it has been found possible, in a few cases, to carry the oxidation to a stage where a long side chain has become only partially oxidized, e.g. aceto-mesitylene,  $\text{C}_6\text{H}_2\text{Me}_3\cdot\text{CO}\cdot\text{CH}_3$ , to mesityl-glyoxylic acid,  $\text{C}_6\text{H}_2\text{Me}_3\cdot\text{CO}\cdot\text{CO}_2\text{H}$ ; *m*-butyl toluene,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{C}_4\text{H}_9$ , by nitric acid at  $180^\circ$ , to *m*-methyl-phenyl-propionic acid,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ .

Cohen and Miller (J. C. S., 1904, 1622) find that compounds containing chlorine or bromine in the meta-position with regard to a methyl group are least readily oxidized by nitric acid, those with similar substituents in the para-position most readily, and those with *o*-substituents are intermediate.

In some cases it is necessary to protect labile groups, e.g.  $\cdot\text{NH}_2$  and  $\cdot\text{CHO}$ , during oxidation. An amino- or imino-group can often be protected by acetylation  $\cdot\text{NHAc}$  or  $\cdot\text{NAc}$ , or even better, by forming the nitroso-derivative,  $\cdot\text{N}\cdot\text{NO}$ . The further oxidation of an aldehydo- to a carboxylic group can often be prevented by the addition of some substance to the oxidizing mixture which will yield a sparingly soluble compound with

the aldehyde; such compounds are a primary aryl-amine, which forms an azomethine, e.g. benzylidene-aniline,  $C_6H_5 \cdot CH : NC_6H_5$ , sodium hydrogen sulphite, or calcium naphthionate, the calcium salt of 1-amino-naphthalene-4-sulphonic acid. From the additive compound to which the last salt gives rise, the aldehyde may be obtained by distillation in steam.

**A. Potassium Permanganate.**—This is the commonest and one of the most useful of oxidizing agents, as it may be used in neutral, alkaline, or acid solution. Other permanganates are also employed, e.g. the calcium and barium salts, especially for the oxidation of complex proteins.

(a) **Alkaline Solution.**—Even when no alkali is added at the beginning, the solution becomes alkaline during the reaction. The permanganate, a derivative of  $Mn_2O_7$ , becomes reduced to hydrated  $MnO_2$ , and thus each molecule of permanganate,  $K_2Mn_2O_8$ , can yield *three* atoms of oxygen:



When the product formed is an acid, this remains dissolved in the alkaline liquid, and may often be obtained by the addition of mineral acid after the manganese dioxide has been removed by filtration. In this manner, numerous benzene hydrocarbons and their derivatives can be oxidized to the corresponding acids, e.g. *p*-chloro-toluene to *p*-chlorobenzoic acid, naphthalene to phthalonic acid,  $o\text{-CO}_2H \cdot C_6H_4 \cdot CO \cdot CO_2H$ . Other examples are the conversion of *o*-nitrophenol into dinitro-dihydroxy-diphenyl,  $NO_2 \cdot (OH)C_6H_3 \cdot C_6H_3(OH) \cdot NO_2$ , and of uric acid into allantoin (p. 330).

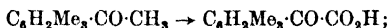
The oxidation of olefine derivatives by 2 per cent permanganate (*Fittig*) is of extreme interest. Two hydroxyl groups are invariably added, and a glycol derivative formed; thus cinnamic acid,  $C_6H_5 \cdot CH : CH \cdot CO_2H$ , yields phenyl-glyceric acid,  $C_6H_5 \cdot CH(OH) \cdot CH(OH) \cdot CO_2H$ . When a stronger permanganate solution or a more powerful oxidizing agent is used, the unsaturated compound is ruptured at the point of the double bond, and a mixture of less complex acids or ketones formed.

Acetone solutions of permanganate are used for oxidizing unsaturated acids or esters (cf. oils and fats, Chap. LV, D.).

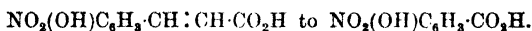
Permanganate and sodium carbonate solution are used for oxidizing aromatic aldehydes to acids.

An excess of alkali is often added to the permanganate before

use. Under these conditions *o*-toluic acid yields phthalic acid, and the method is largely made use of for oxidizing *o*-substituted derivatives of toluene, &c. When the solution is dilute and the temperature is kept at 0°, the oxidation is mild, and can stop at the formation of a glyoxylic acid, e.g.:



otherwise a substituted benzoic acid—in this case  $\text{C}_6\text{H}_2\text{Me}_3\cdot\text{CO}_2\text{H}$ —is always formed. Substituted cinnamic acids, by this method, can be converted into corresponding benzoic acids, e.g.:



Similarly, hydrocarbons of the type of triphenyl-methane,  $\text{CHPh}_3$ , can be oxidized to carbinols, e.g.  $\text{CPh}_3\cdot\text{OH}$ , and compounds of the type of diphenyl-methane,  $\text{CH}_2\text{Ph}_2$ , to ketones,  $\text{CPh}_2\cdot\text{CO}$ .

Caution is required in deducing structures from data obtained by oxidations with strongly alkaline permanganate. This is especially necessary with unsaturated compounds where the alkali can effect a shifting of the double bond, or in polyhydroxy compounds as the ketones formed, reacting as enols, can undergo a shift of the olefine bond (*Farmer, C. and I., 1937, 469*).

(b) **Neutral Solution.**—In a few cases it is necessary to keep the solution neutral from beginning to end, and this is accomplished by the addition of an excess of magnesium sulphate, which yields insoluble magnesium hydroxide with the caustic potash produced during the oxidation. When acet-*o*-toluidide,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ , is thus oxidized, an 80 per cent yield of acetanthranilic acid,  $\text{CO}_2\text{H}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ , is formed, whereas in the presence of alkali the yield is only some 30 per cent.

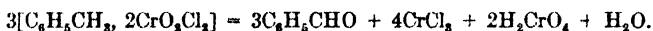
(c) **Acid Solution.**—Acetic or sulphuric acid is used, and the acid is added gradually with the permanganate. The method is of use for the preparation of very stable compounds only, as the majority are completely decomposed by these reagents. The reaction is quite different from that in alkaline solution, the permanganate (a derivative of  $\text{Mn}_2\text{O}_7$ ) is reduced to a manganous salt (derived from  $\text{MnO}$ ), and thus each molecule of permanganate gives rise to *five* atoms of available oxygen:



Sulphides or hydrosulphides in both the aliphatic and aromatic series may be oxidized to sulphonic acids, a reaction which is useful for the preparation of certain naphthalene-sulphonic acids which cannot be obtained by direct sulphonation. *o*-Iodo-benzoic acid may be oxidized to *o*-iodoso-benzoic acid, tetrabromo-*p*-xylene to tetrabromo-terephthalic acid, and primary alcohols to aldehydes.

**B. Chromic Acid Derivatives.**—**Chromic anhydride**,  $\text{CrO}_3$ , is often used as an oxidizing agent when dissolved in glacial acetic acid, two molecules of the anhydride yielding three atoms of oxygen,  $2\text{CrO}_3 = \text{Cr}_2\text{O}_3 + 3\text{O}$ . Usually only the theoretical amount required for the oxidation is used, and this is gradually run in from a dropping funnel. Quinoline homologues are oxidized to quinoline-carboxylic acids, and aromatic alcohols to aldehydes, if a primary amine is present to form a *Schiff's* base with the latter (p. 493). Even benzene homologues may be oxidized to aldehydes in the presence of acetic anhydride, as the acetyl derivatives thus formed are stable.

**Chromyl chloride**,  $\text{CrO}_2\text{Cl}_2$ , the chloride of chromic acid, is used for oxidizing benzene hydrocarbons to aldehydes (*Etard's* reaction, Chap. XXV, B.). The usual method is to dissolve the hydrocarbon and chromyl chloride separately in carbon disulphide, and to run in the chloride solution until the red colour persists, and then to decompose with water. A precipitate of a double compound, e.g.  $\text{C}_6\text{H}_5\cdot\text{CH}_3, 2\text{CrO}_2\text{Cl}_2$ , is first produced, and this is decomposed by water according to the equation:



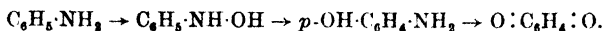
The usual method of using chromic acid is in the form of a mixture of a **dichromate** and **sulphuric acid**, which react according to the equation:



each molecule of dichromate yielding three atoms of available oxygen. Sometimes potassium dichromate is used, but more frequently the sodium salt, as it is cheaper and more readily soluble in water. As a rule, the dichromate mixture is added gradually to the oxidizable substance. It is the common method of preparing aldehydes from alcohols (Chap. V, A.), and also from aromatic hydrocarbons, as there is not the same tendency for the  $\cdot\text{CHO}$  group to be further oxidized as when permanganate is employed. Complex alcohols may also be

oxidized to ketones or aldehydes, e.g. menthol to menthone (Chap. LVII, B2). Many compounds, such as hydroxy acids, ketones, ketonic acids, &c., are ruptured by chromic acid mixture, and acids or ketones containing a smaller number of carbon atoms are formed.

This is the oxidizing agent usually employed for the preparation of quinones, e.g. from aniline, and as a rule the temperature should be kept at about 0°. According to *Bamberger*, the following series of reactions occur:



**C. Nitric Acid.**—Examples of the complete oxidizing action of fuming nitric acid are met with in the ordinary *Carius* method for estimating halogens or sulphur. One of the chief drawbacks of nitric acid is, that in addition to being an oxidizing agent, it is also a nitrating agent, and the products of oxidation, even when dilute acid is used, contain smaller or larger amounts of nitro-derivatives. It is used for oxidizing aldehydes, particularly halogen substituted aliphatic, to acids, and also of polyhydroxy aliphatic aldehydes. By means of dilute nitric acid many benzene homologues are oxidized to carboxylic acids, but the process is slow; thus pentamethyl benzene dissolved in benzene requires sixty hours' boiling to oxidize it to tetramethyl-benzoic acid, and slightly longer time is required to oxidize 2:6-chloro-nitro-toluene to the corresponding acid. An interesting oxidation is that of *m*-butyl-toluene to *m*-methyl-phenyl-propionic acid,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , and a somewhat complex oxidation is that of camphor to camphoronic acid (Chap. LVII, C2). *Krafft* (B., 1889, 2735) introduced the use of concentrated nitric acid (sp. gr. 1.5) for oxidizing purposes. The admixture was effected at 0°–10°, the temperature gradually raised to 50°, and the product poured into water. This is a very good method for oxidizing compounds which are already nitrated, but in other cases nitro-derivatives are very liable to be formed. Dinitroxy-lene is oxidized in this way to dinitrophthalic acid. Sulphoxides, e.g.  $\text{Et}_2\text{SO}$ , may be oxidized to sulphones,  $\text{Et}_2\text{SO}_2$ , iodo-benzoic acid to iodoso-benzoic acid, cane-sugar to oxalic acid, &c. The method adopted in oxidizing glycerol to glyceric acid is to allow the aqueous solution of the glycerol to float on concentrated nitric acid.

A mixture of concentrated nitric and sulphuric acids, which

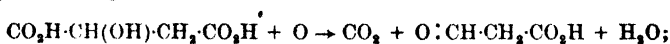
is an extremely good nitrating agent, may be used for oxidizing purposes, e.g. *o*-nitro-benzyl alcohol to the corresponding aldehyde, of *p*-nitro-cinnamic acid to *p*-nitro-benzaldehyde, and of *s*-trinitro-toluene to *s*-trinitro-benzoic acid.

**D. Sulphuric Acid.**—One of the oldest examples of the oxidizing action of concentrated sulphuric acid is the conversion of ethyl mercaptan,  $C_2H_5SH$ , to ethyl disulphide,  $(C_2H_5)_2S_2$ , and another that of piperidine to pyridine. *Schmidt* introduced the use of fuming sulphuric acid (60 or 70 per cent  $SO_3$ ) at low temperatures for converting alizarin and other hydroxy-derivatives of anthraquinone into tri- to hexahydroxy-derivatives, many of which are important dyes. The hydroxy-groups form an ester with the sulphuric acid, but this is readily hydrolysed when boiled with dilute acid. Concentrated sulphuric acid may also be used for the preparation of the same compounds, and the yields are largely increased by the addition of boric acid, this being probably due to the fact that boric esters are formed, which prevent the removal of the hydroxy-groups when once introduced.

An oxidizing action of interest is the conversion of naphthalene into phthalic acid by means of concentrated sulphuric acid and a small amount of mercuric sulphate at a temperature above  $300^\circ$ .

**Selenium dioxide**,  $SeO_2$ , the analogue of  $SO_2$ , can oxidize 5-methylacridine to acridine-5-aldehyde in acetic acid solution.

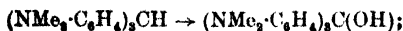
**E. Peroxides.**—The peroxides mainly employed are  $MnO_2$ ,  $PbO_2$ , and occasionally  $H_2O_2$ . **Lead peroxide** is frequently used in the form of a paste with acetic acid, one of the earliest oxidations with this reagent being that of uric acid to allantoin (p. 330). Characteristic oxidations are (i) that of  $\alpha$ -hydroxy acids to aldehydo-acids, with one less carbon atom (p. 344), e.g.:



(ii) of alkyl acetates to aldehydes, e.g.:



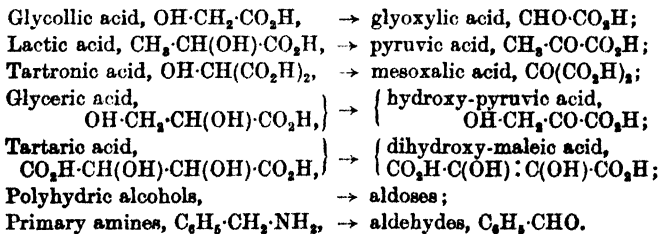
(iii) of triphenyl-methane-derivatives to the corresponding carbinols, the salts of which are dyes, e.g.:





and (iv) of amino-hydroxy-derivatives of anthraquinone to the corresponding polyhydroxy-derivatives, the  $\text{NH}_2$  being replaced by  $\text{OH}$ , a reaction which does not occur when the amino-group is acetylated. **Lead tetracetate**,  $\text{Pb}(\text{OAc})_4$ , is extremely useful for oxidizing sugars and derivatives. **Manganese dioxide** alone, or in the presence of sulphuric acid, may be used for converting  $\text{CH}_3$  groups in benzene homologues into aldehydo-groups. The mixture is kept stirred, and an excess of hydrocarbon is always present. Benzaldehyde, *o*-chloro-benzaldehyde, *p*-nitro-benzaldehyde, terephthalic aldehyde, &c., have been prepared by this method. A remarkable oxidation is that of benzene to benzoic acid by means of the peroxide and sulphuric acid. Hydroxy acids are often ruptured by these reagents, e.g. lactic acid,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$ , yields aldehyde and carbonic acid. This is the basis of a method for estimating the strength of solutions of lactic acid by determining the amount of aldehyde formed. The same reagents are also used for the oxidation of alkaloids, and for the conversion of the leuco-bases of triphenyl-methane dyes into the dye salts, e.g. *p*-leucaniline into *p*-rosaniline. **Perhydrol** is often used in the presence of potassium hydroxide for the preparation of organic peroxides, e.g. diethyl-peroxide,  $\text{Et}_2\text{O}_2$ , benzoyl-peroxide,  $(\text{C}_6\text{H}_5\text{CO})_2\text{O}_2$ . Piperidine, when oxidized with 3 per cent peroxide solution, yields glutaric acid owing to the rupture of the ring. Benzene, with the peroxide, yields a certain amount of phenol. Azo-compounds are converted into corresponding azoxy-derivatives, and phenols into dihydric phenols or quinones. Fatty acids are converted into ketones,  $\text{R}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OH} \rightarrow \text{R}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\text{R}$  (*Dakin*, Am. C. J., 1910, **44**, 41).

*Fenton* and others (J. C. S., 1894, 899; 1895, 48, 774; 1899, 1) have made use of perhydrol in the presence of small amounts of ferrous salts; by this method the following reactions have been effected:



**F. Oxygen** itself can often be used for oxidation, generally in the presence of platinum black or platinized asbestos (cf. Catalytic Oxidation and Dehydrogenation, Chap. XLIX, C).

Many aldehydes, when exposed to moist air, are transformed into acids; thus specimens of benzaldehyde which have been kept for some time contain appreciable amounts of benzoic acid.

This oxidation is photochemically activated and is characterized by an induction period in which oxygen is absorbed but no benzoic acid formed. Certain catalysts, e.g. activated surfaces, reduce this period, and it is highly probable that an additive compound of benzaldehyde and oxygen, viz. per-

benzoic acid (p. 516) benzoylperhydrol,  $\text{C}_6\text{H}_5\text{-C}\begin{array}{c} \text{O} \\ \diagup \\ \text{O-OH} \end{array}$ , which is

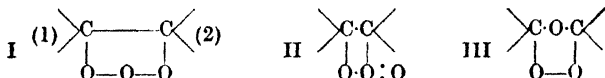
the actual oxidizing agent converting the aldehyde into benzoic acid.

**G. Ozone-Ozonides.**—Ozone may also be used as an oxidizing agent; it is employed commercially for refining oils, &c. (cf. J. S. C. I., 1898, 1101). *C. Harries* (A., 1905, **343**, 311; 1910, **374**, 288; 1912, **390**, 235; 1915, **410**, 1) has examined the action of ozone on various types of carbon compounds, mainly in glacial acetic acid solution. Methane, ethyl alcohol, &c., are oxidized to aldehydes and acids, hydrogen peroxide also being formed. Saturated aldehydes and, to a certain extent, ketones yield labile peroxides of the type,  $\text{R-CH:O:O}$ . Most unsaturated hydrocarbons and alcohols combine with ozone in suitable solvents, e.g. saturated hydrocarbons or alkyl halides, yielding ozonides, e.g. *ethylene ozonide*,  $\text{C}_2\text{H}_4\text{O}_3$ , *allyl alcohol ozonide*,  $\text{C}_3\text{H}_5\text{-OH, O}_3$ , and for each ethylene linking one molecule of ozone is added. Many compounds combine with more than this amount of ozone, yielding **oxozonides**, e.g. propylene yields a product,  $\text{C}_3\text{H}_6 + \text{O}_4$ , which are not readily transformed into normal ozonides. They are regarded as derived from **oxozone**,  $\text{O}_4$ , which has been shown to be present in ordinary ozone, and hence it is always desirable to purify ozone by passing it through alkali and concentrated sulphuric acid before using it for the preparation of ozonides proper.

After removal of the solvent the ozonides are obtained as oils, syrups, or glassy solids, and in a few cases only as crystalline solids. Some are volatile, but most are extremely unstable, and even highly explosive and hence difficult to prepare. They

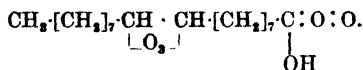
dissolve in most organic solvents, but tend to decompose in contact with water.

The structure of these compounds suggested by *Harries* is shown in formula I, but more recently *Standinger* (B., 1925, 1088) has suggested that the ozonide first formed (**molozone**) has the structure indicated by formula II, and that this then polymerizes as in the case of cyclohexene or isomerizes to an iso-ozonide, formula III (cf. A., 1937, 529, 33), and to this latter group belong the stable distillable ozonides.

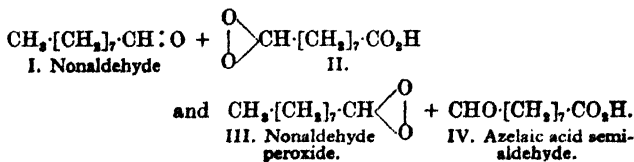


This structure is in harmony with the formation of carbonyl compounds (aldehydes or ketones) and not glycols on reduction of the stable ozonides. The tendency to polymerization is most marked where the olefine linking is present in a ring structure, acetic acid appears to favour the isomerization to the iso-form, whereas solvents which favour association cause polymerization. If the original olefine compound is not symmetric two isomeric malozonides are theoretically possible.

Unsaturated carbonyl derivatives, e.g. acids, aldehydes, and ketones, also combine with ozone, yielding ozonides; they can, however, combine with a fourth atom of oxygen, yielding **perozonides**, which are decomposed by water, yielding the ozonide and hydrogen peroxide. The three atoms of the ozonide are regarded as attached to the two carbon atoms of the ethylene linking, whilst the fourth atom is attached to the carbonyl group. Oleic acid perozonide is represented as:



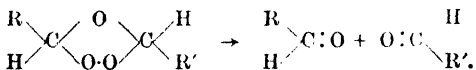
The ozonides are decomposed, undergo **ozonolysis**, when gently heated, or when the solutions in glacial acetic acid are warmed. Oleic acid ozonide decomposes into the four products:



The compounds containing the aldehydo-group, CHO, undergo oxidation to the corresponding acids, i.e. I and IV yield respectively nononic acid, a monobasic acid, and azelaic acid, a dibasic acid. Similarly the aldehyde peroxide group isomerizes to the carboxylic group so that II and III are transformed to azelaic and nononic acid. The main products of ozonolysis are therefore a monobasic acid, nononic acid, and a dibasic acid, azelaic acid, both normal and containing 9 carbon atoms. These are fairly easily separated and obtained pure, and hence the position of the olefine link between carbon atom 9 and 10 is established and oleic acid is  $\Delta^9$ -octa-decenoic acid. The nonaldehyde peroxide formed in this way is isomeric, and not identical with the peroxide obtained by the direct action of ozone on the aldehyde. It is more stable, has m.-pt.  $73^\circ$ , and is represented by formula III.

This method of ozonolysis is used for determining the position of the ethylene linking in the molecule of the unsaturated compound, and also for the preparation of certain aldehydes, aldehydic acids, and dialdehydes.

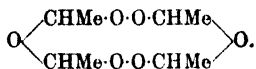
Another method also used is the reduction of the ozonide with hydrogen and palladized calcium carbonate at comparatively low temperatures (B., 1932, 1467):



Similarly with a diolefine,



the product is a mixture of two mono- and one di-aldehyde. Sym. butylene ozonide is dimeric and probably has the ring structure:

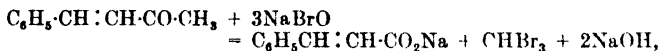


Benzene yields a highly explosive triozone,  $\text{C}_6\text{H}_6\text{O}_3$ . With naphthalene one ring adds on ozone more readily than the other, yielding  $\text{C}_{10}\text{H}_8\text{O}_6$ .

Ozonized oxygen in the presence of concentrated sulphuric acid converts toluene at  $100^\circ$  into benzoic acid.

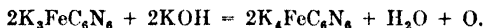
**H. Other Oxidizing Agents.**—Chlorine and bromine are generally used in alkaline solution, i.e. in the form of hypo-

chlorite or hypobromite. As examples, we have the well-known *Hofmann* reaction, the conversion of amides, and imides such as succinimide and phthalimide, into amines or nitriles (pp. 211 and 212); also the oxidation of reduced benzene derivatives back to the original benzene compound. An interesting oxidation is that of benzylidene-acetone to cinnamic acid with 4 per cent sodium hypobromite:



and of potassium cyanide to cyanate by hypochlorite. Bromine water itself is frequently used for the oxidation of sugars, e.g. of an aldose to the corresponding monobasic acid; thus glycero- to glyceric acid, glucose to gluconic acid.

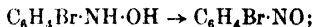
Less common oxidizing agents are **potassium ferricyanide**, which is reduced to the ferrocyanide:



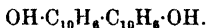
*s*-Trinitro-benzene may be oxidized by this reagent to picric acid, phenyl-acetylene to diphenyl-diacetylene,  $\text{CPh:C:C:CPh}$ , nitroso- to nitro-derivatives, quinone-dioxime to dinitroso-benzene, benzene-diazo-oxides to salts of benzene-diazoic acid,  $\text{C}_6\text{H}_5\text{:N:NO}\cdot\text{OH}$ , and nitro-toluenes to nitro-benzoic acids. **Ferric chloride**,



may be used for oxidizing hydroxylamine derivatives to nitroso-compounds, e.g.:



quinols to quinones, and naphthols to dinaphthols:

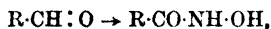


**Silver oxide** oxidizes glycerol to glycollic acid, and generally aldehydes to acids (C. R., 1909, 149, 39), unsaturated aldehydes and amino-aldehydes to acids (B., 1913, 2510), and *o*-dihydroxy-benzene to *o*-benzo-quinone. In the presence of sodium or ammonium hydroxides silver oxide only oxidizes those compounds containing a  $\text{CH}\cdot\text{OH}$  or  $\text{CO}$  group attached to two  $\text{CH}_2\cdot\text{OH}$ ,  $\text{CH}\cdot\text{OH}$ , or  $\text{CO}_2\text{H}$  groups or combination of these, e.g. tartaric acid, glycerol, and mannitol. In neutral or acid solution it is sufficient if the  $\text{CH}\cdot\text{OH}$  group is combined

with  $\text{CO}_2\text{H}$  and with  $\text{H}$ ,  $\text{CH}_2$ , or  $\text{CH}_3$ , e.g. glycollic, lactic, and malic acids. **Mercuric oxide**, usually with alkali, e.g. barium hydroxide, is used for oxidizing fructose to trihydroxy-butyric acid and glycollic acid, and glucose to gluconic acid. It also oxidizes unsym. diethyl-hydrazine to tetraethyl-tetrazone,  $\text{NEt}_2\text{:N:N:NEt}_2$ , and sym.-diethyl-hydrazine to mercury-diethyl nitrogen, and water. **Nitro-benzene** is used as an oxidizing agent in the manufacture of magenta (p. 559), and also in the *Skraup* synthesis of quinoline (p. 692). **Potassium persulphate**, mixed with concentrated sulphuric acid, is known as *Caro's* reagent or sulphomono-per-acid, and can oxidize salicylic acid to 2:5-dihydroxy-benzoic acid, and salicaldehyde to 2:5-dihydroxy-benzaldehyde. It is also used for oxidizing various terpene derivatives, and readily oxidizes aromatic primary amines to nitroso-derivatives, e.g.:

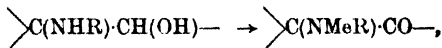


**Sodium nitrohydroxylamine**,  $\text{Na}_2\text{N}_2\text{O}_3$ , reacts with an aldehyde in the presence of alkali, giving a hydroxamic acid,



which on hydrolysis gives the carboxylic acid.

**Formaldehyde.**—When certain amino alcohols are methylated by means of formaldehyde, it has been found that not merely is the  $\text{CH}_3$  group introduced, but at the same time the alcohol is oxidized to an aldehyde or ketone, thus in the case of many cyclic compounds (*Hess*, B., 1913, 4104; 1915, 1886),



e.g. 3- $\alpha$ -hydroxy-ethyl-pyrrolidine gives 1-methyl-pyrrolidine-3-acetaldehyde.

**I. Electrolytic Oxidation.**—Organic compounds may be oxidized by means of the oxygen formed at the anode of an electrolytic cell. The method is not so general in application as electrolytic reduction, as it is extremely difficult to stop the reaction at the right point. Even when the theoretical amount of oxygen has been formed, it is often found that part of the compound is unacted on, and part has been completely oxidized. The following are fairly typical examples:

**Purpuro-gallin** is formed by the electrolysis of a solution of pyrogallol in sodium sulphate solution, using a rotating

platinum anode of 2 sq. dm. The reaction is complete after 6–8 hours with a C.D. of 1.5–2 amperes and an E.M.F. of 4.3–4.5 volts.

**Anthraquinone** may be prepared by oxidizing an emulsion of anthracene, water, and sulphuric acid, using a rotating lead cathode, and a leaden vessel as anode. The best yields are obtained when an oxygen carrier, e.g. manganese sulphate, is employed with a temperature of 75°–90°, a C.D. of 1–2 amperes, and an E.M.F. of 2.8–3.5 volts.

Numerous azo-dyes have been obtained electrolytically; thus **Orange II**, or  $\beta$ -naphthol-azobenzene-sulphonic acid,  $\text{OH}\cdot\text{SO}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{N}\cdot\text{C}_{10}\text{H}_6\cdot\text{OH}$  (Chap. LIX, B1), is produced from an aqueous solution containing sodium sulphanilate,  $\beta$ -naphthol, and sodium nitrite. The cathodes of nickel or platinum wire are placed in two separate cathodic compartments consisting of small porous cells and containing sodium hydroxide solution. The rotating anode is of platinum; and a C.D. of 8–12 amperes, an E.M.F. of 15–18 volts, and as low a temperature as possible, give the best results. The homologues of benzene, when oxidized with platinum electrodes in the presence of sulphuric acid and acetone, yield aldehydes, e.g. toluene  $\rightarrow$  benzaldehyde, *o*-xylene  $\rightarrow$  *o*-toluic-aldehyde, but the yields, as a rule, are not good. Ortho-substituents of a negative character tend to inhibit such oxidations. Acetic acid solutions of *p*- and *o*-nitro-toluenes yield the corresponding nitro-benzyl alcohols, whereas the *m*-compound yields *m*-nitro-benzaldehyde. Benzyl sulphide yields benzylsulphoxide, benzylsulphoxide, or tribenzylsulphonium sulphate according to conditions.

**J. Autoxidation.**—Turpentine and numerous other olefine compounds can absorb oxygen from the air and render it so active that it can oxidize a second substance which normally would not be oxidized in the absence of turpentine. For example air readily bleaches indigo or oxidizes arsenious acid in the presence of turpentine. The reaction can be photochemically activated, and it is highly probable that molecular oxygen attaches itself to the olefine linking, forming a mol-

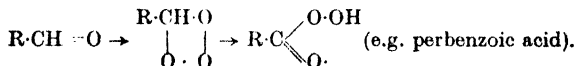
oxide,  $\text{RH}\cdot\text{C}=\text{CHR}$   
 $\begin{array}{c} | \quad | \\ \text{O} \quad \text{O} \end{array}$ , which is the autoxidator. Some of these

can be kept in the dark and at low temperatures for years, e.g. pinenemoloxide, others decompose very rapidly and may

explode. The normal fission would be into 2 molecules of ketone, but in the presence of a readily oxidizable substance they give up oxygen to this (the acceptor); in the above cases the indigo or arsenious acid.

For recent views, especially with reference to autoxidation of ketens, see *Standinger*, B., 1925, 1075.

Similarly in the addition of oxygen to an aldehyde:



For oxidations by means of micro-organisms see Chap. LXIX. B. and C.

## XLIX. CATALYTIC ACTION OF FINELY DIVIDED METALS AND METALLIC OXIDES

### A. Catalytic Reduction or Hydrogenation \*

Numerous reductions by means of gaseous hydrogen can be readily accomplished by using a suitable catalyst. The reduction may take place in the vapour phase at moderate or high temperatures, in the liquid phase at room temperature or temperatures up to 300°–400°, but usually at 160°–250°, and in either liquid or vapour phase at atmospheric pressure or at pressures up to several hundred atmospheres. As the reductions decrease the volume they are helped by increased pressure.

*Sabatier* and *Senderens* (1897–1919) in their study of the action of finely divided metals found that platinum is an extremely efficient catalyst, but that nickel, cobalt, copper and iron can also be used, but of these nickel is much the best.

In more recent years mixed catalysts have been used, e.g. copper chromite (CuO and Cr<sub>2</sub>O<sub>3</sub>).

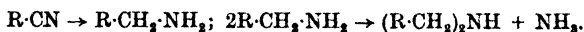
\* *Hydrogenation of Organic Substances*, C. Ellis, New York, 1930. *The Mechanism of Contact Catalysis*, E. H. Griffiths, Oxford, 1936.



**Nickel.**—The metal must be in an extremely fine state of division, and this is accomplished by reducing the metallic oxide in a current of hydrogen at a temperature of about  $300^{\circ}$ . A few grams of the metal are usually sufficient and it retains its activity for a long time. In some cases it is advisable to deposit the nickel on a suitable medium such as infusorial earth, pumice, asbestos, or a membrane. When infusorial earth is used as a support, it is found that in aqueous or aqueous-alcoholic solutions reduction occurs at the ordinary temperature (B., 1916, 55).

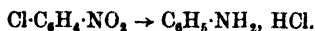
Of the numerous reductions which have been accomplished by this process, may be mentioned the following: Carbon monoxide at  $200^{\circ}$  and carbon dioxide at  $300^{\circ}$  are reduced to methane and water. Aromatic hydrocarbons, e.g. benzene, toluene, xylene, cymene, at  $180^{\circ}$  yield their hexahydro-derivatives. Ethyl-benzene reacts in a somewhat curious manner; it appears to be first reduced to its hexahydro-derivative,  $C_6H_{11}\cdot C_2H_5$ , but this is partially reduced to  $C_6H_{11}\cdot CH_3$  and  $CH_4$ . Similarly phenyl-acetylene,  $C_6H_5\cdot C\equiv CH$ , yields a mixture of ethyl-cyclohexane, methyl-cyclohexane, and methane. The terpenes—limonene, sylvestrene, terpinene, menthene—all yield *p*-methyl-isopropyl-cyclohexane. Pinene yields a dihydro-derivative and naphthalene a tetrahydro-compound, and this with more hydrogen, decahydro-naphthalene,  $C_{18}H_{10}$  (Leroux).

Aliphatic nitriles at  $180^{\circ}$ – $200^{\circ}$  yield primary amines, and finally secondary and tertiary amines and ammonia:



Aromatic nitriles yield ammonia and an aromatic hydrocarbon:  $C_6H_5CN + 3H_2 = C_6H_5\cdot CH_3 + NH_3$ .

Aromatic chloro-derivatives are readily dehalogenized at temperatures above  $270^{\circ}$ :  $C_6H_5Cl \rightarrow C_6H_6$ , and similarly for polychloro-derivatives. The presence of  $CH_3$ ,  $OH$ , and  $NH_2$  groups appears to facilitate reduction:



Aliphatic nitro-compounds at  $150^{\circ}$ – $180^{\circ}$  yield the corresponding primary amines, but at higher temperatures paraffins and ammonia. Aromatic nitro-compounds are best reduced in presence of copper at  $300^{\circ}$ – $400^{\circ}$ ; in this manner nitro-benzene yields aniline and  $\alpha$ -nitro-naphthalene  $\alpha$ -naphthylamine and *o*-nitro-phenol *o*-amino-phenol; whereas, when nickel

is used,  $\alpha$ -nitro-naphthalene yields ammonia and tetrahydro-naphthalene.

Phenol, *o*-cresol, thymol, and carvacrol at 170°–180° are reduced to their hexahydro-derivatives, as are also methyl- and ethyl-anilines. Aniline at 190° also yields its hexahydro-derivative, cyclohexylamine,  $C_6H_{11}NH_2$ , but at the same time dicyclohexylamine,  $(C_6H_{11})_2NH$ , and cyclohexyl-aniline,  $C_6H_{11}NH \cdot C_6H_5$ , are produced. *Schiff's* bases (p. 493) and reduced nickel at 200°–230° give hydrocarbons and secondary amines, e.g.  $Ph \cdot NH \cdot CH_2Ph$  from benzylideneaniline, together with a little aromatic hydrocarbon (toluene) and base (aniline) (*Maihle*, Bull. Soc., 1919, **25**, 321).

At moderate temperatures (130°–160°) polyhydric phenols yield corresponding hexahydro-derivatives.

Alcohols are formed by the reduction of aldehydes and ketones at temperatures slightly above their boiling-points, e.g.  $(C_2H_5)_2CO \rightarrow (C_2H_5)_2CH \cdot OH$ .

Olefine and acetylene derivatives are readily transformed into the corresponding saturated compounds at moderate temperatures, and compounds of the aromatic series, e.g. cinnamic acid, can be reduced to saturated compounds without the benzene nucleus being effected. Unsaturated ketones, e.g. mesityl oxide and phorone, can be reduced to the corresponding saturated ketones. Diketones yield various products: thus diacetyl at 140°–150° yields a mixture of hydroxy-ketone and glycol; acetylacetone yields the anhydride of the corresponding glycol; benzil, benzoin, and benzoylacetone yield the corresponding hydrocarbons. Lævulic acid yields valerolactone, quinones yield quinols; and carbylamines, alkyl isocyanates, and oximes yield mixtures of amines, mainly secondary. (*Sabatier* and *Senderens*, Annales, 1905 [viii], **4**, 319; *Sabatier* and *Maihle*, *ibid.* 1909, **16**, 70; *Sabatier*, B., 1911, 1984.)

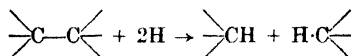
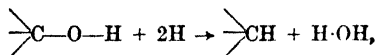
With a slightly active nickel at 300°–350°, ketones of the type benzophenone and phenyl benzyl ketone yield the aromatic hydrocarbons, e.g. diphenylmethane and *s*-diphenylethane. With a more active nickel at 170°, the benzene nuclei are also reduced (*Sabatier* and *Murat*, C. R., 1914, **158**, 760).

According to *Boeseken* and *van Senden* (Rec. trav., 1913, **32**, 23), both heptaldehyde and *n*-heptyl alcohol when heated with nickel at 220° yield *n*-hexane together with CO.

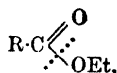
The following saturated monohydric alcohols when reduced

with hydrogen at 250° and under pressures of 100–200 atmospheres yield methane, water and a saturated hydrocarbon containing one atom of carbon less than the original alcohol: *n*-dodecyl, *n*-tetradecyl, *n*-octadecyl and  $\gamma$ -cyclohexylpropyl. With secondary alcohols, e.g. octan-2-ol and *cyclo*-hexanol, the corresponding hydrocarbons *n*-octane and *cyclo*-hexane are formed.

When a copper chromite catalyst is used at temperatures 120°–250° and pressures of 140–210 atmospheres many oxygen and even carbon compounds undergo fission (hydrogenolysis analogous to hydrolysis),



The following compounds undergo fission at the link indicated.



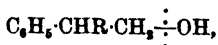
Esters of saturated acids.



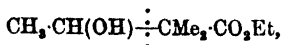
Esters of  $\beta$ -hydroxy acids.



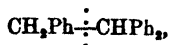
Substituted benzyl alcohols.



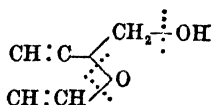
$\beta$ -phenyl- $\beta$ -alkyl ethanols.



Ester of  $\alpha\alpha$ -dimethyl- $\beta$ -hydroxy propionic acid.

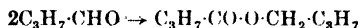


$\alpha\alpha\beta$ -triphenyl ethane.



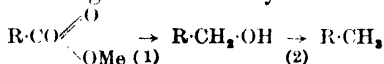
also open-chain and cyclic glycols and malonic and acetoacetic esters.

When the vapour of an alcohol is passed over the same catalyst in the absence of hydrogen at 300° at atmospheric pressure, the reaction is largely dehydrogenation, e.g. butyl alcohol yields butaldehyde and hydrogen, but at 300°–400° and at pressures of 100–300 atmospheres the aldehyde condenses to an aldol and then dehydration to an unsaturated aldehyde (croton-aldehyde) or to an ester, e.g. *n*-butylpropionate:



(*Atkins* and others, J. A. C. S., 1932, 4678; 1933, 2992).

Hydrocarbons can be prepared from esters by a two-stage catalytic hydrogenation process. The ester is first reduced to the alcohol using a copper-chromite catalyst, and then to the hydrocarbon using a nickel catalyst.



(*ibid.* 1933, 1293).

**Platinum.**—*Willstätter* and others (B., 1912, 1471; 1913, 527; 1918, 769) used platinum black and hydrogen for reducing numerous benzene derivatives although they are reduced less readily than olefines. The method is to shake the mixture in presence of glacial acetic acid at room temperature and pressure. The main products are the corresponding cyclohexyl compounds (addition of 6H), but with phenol a certain amount of cyclohexane is also formed and with aniline ammonia and dicyclohexylamine are also obtained. Naphthalene appears to be reduced directly to decalin as no di- or tetra-hydro-compounds can be isolated. Dihydro-naphthalene under similar conditions yields the tetra-hydro-compound and then more slowly decalin.

In the presence of small amounts of oxygen phthalic an-

hydride yields phthalide,  $\text{C}_6\text{H}_4 \begin{array}{c} \text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CO} \end{array} \text{O}$ , *o*-toluic acid and

finally hexahydrophthalide and cyclohexane-1 : 2-dicarboxylic acid indicating that the anhydride ring is reduced more readily than the benzene ring. Traces of phthalic anhydride inhibit the reduction of benzene unless the metal is activated by oxygen, and phthalic acid itself is readily reduced in the absence of oxygen and all traces of the anhydride. On the other hand,

the presence of oxygen retards the reduction of pyrrole derivatives (*Hess*, B., 1913, 3113). For the reduction of acetylenes platinum is less effective than palladium (*Paal*, 1918, 640).

With a platinum catalyst and the ketonic esters  $\text{CH}_3\cdot\text{CO}[\text{CH}_2]_n\cdot\text{CO}_2\text{Et}$  (where  $n = 1$  to 5) the rate of reduction of CO decreases as  $n$  increases, but with lævulic esters  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{R}$  it decreases as R increases (*J. A. C. S.*, 1931, 3861; 1933, 806).

**Palladium.**—Colloidal platinum has been used for reducing nitrobenzene in alcoholic solution at  $65^\circ$ – $85^\circ$ , and a yield of 50 per cent of aniline obtained (B., 1907, 2209), but colloidal palladium has found more general use, e.g. for reducing alcoholic solutions of unsaturated acids or their esters or glycerides at ordinary temperature (*Paul and Gerum*, B., 1908, 2273; 1909, 1553, 2244, 3930). For preparation of colloidal palladium on activated charcoal cf. B., 1924, 1263. Similarly unsaturated ketones can be reduced to saturated, e.g. citral yields citronellal and citronellol, and many alkaloids also take up hydrogen (B., 1909, 1627; 1911, 2862). By altering the pressure of the hydrogen it is sometimes possible to obtain from an unsaturated ketone either the saturated ketone or the secondary alcohol. With a pressure of 1–2 atmospheres *d*-palegone yields *d*-menthone, mesityl oxide yields methyl-isobutyl ketone, but phorone yields di-isobutyl carbinol unless a pressure of less than 1 atmosphere is used when the saturated ketone is formed. With a pressure of 5 atmospheres cyclic ketones and aromatic aldehydes are reduced to alcohols (*Skita*, B., 1910, 3393), and even solutions of palladous chloride in hydrochloric acid can be used in place of the colloidal metal (1911, 2862).

Palladium deposited on active charcoal (B., 1924, 1263, or *J. S. C. I.*, 1936, 225T) is often used, e.g. in determining the hydrogen value of polyenes, the reduction being complete at room temperature and pressure in a short time. If platinum is substituted for palladium the benzene ring can be reduced at the same time. Ketones of the type acetophenone and its homologues are readily reduced to hydrocarbons with a palladium-charcoal catalyst (*Zelinsky* and others, B., 1933, 872). This does not, however, apply to cyclic ketones, to hexahydroacetophenone and its homologues, or to ketones in which the CO is separated from the benzene ring by  $\text{CH}_2$  or  $\text{CH}_2\cdot\text{CH}_2$ . With benzoin the CO is reduced before the OH, and the stages

are  $\text{Ph}\cdot\text{CO}\cdot\text{CHPh}\cdot\text{OH} \rightarrow \text{OH}\cdot\text{CHPh}\cdot\text{CHPh}\cdot\text{OH}$ ,  $\text{CH}_2\text{Ph}\cdot\text{CH}_2\text{Ph}$ . The chlorides of dibasic acids with the same catalyst give aldehyde acids,  $\text{CHO}\cdot(\text{CH}_2)_n\cdot\text{CO}_2\text{H}$ .

With quaternary ammonium salts a hydrocarbon and tertiary amine are formed, e.g.  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{NMe}_2\text{PhCl}$  gives toluene and dimethylaniline (Helv., 1932, 1330).

Hydrogen and palladinized charcoal have been used for reducing aminoalkylketones, e.g.  $\text{R}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{NH}_2$ , to the corresponding carbinols,  $\text{R}\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{NH}_2$  (Arch. pharm., 1915, 253, 181), and palladinized barium sulphate and hydrogen reduce acid chlorides to aldehydes (Chap. VII, B.). Palladium or platinum in a fine state of division, e.g. deposited on barium sulphate, or infusorial earth, reduces unsaturated alcohols, aldehydes of the open-chain terpene series to the corresponding saturated analogues without destroying the  $\text{CH}_2\cdot\text{OH}$ ,  $\text{CHO}$ , or  $\text{CO}_2\text{H}$  groups (Paal, Chem. Zeit., 1917, ii, 145).

When aromatic alcohols, aldehydes, or ketones are reduced catalytically in acetic acid solution in the presence of colloidal platinum, the products are usually hydrocarbons, e.g. benzaldehyde yields toluene and its hexahydro-derivative. If the  $\text{OH}$ ,  $\text{CHO}$ , or  $\text{CO}$  groups are protected, then their hexahydro-derivatives are formed, e.g. benzylideneaniline gives hexahydro-benzaldehyde,  $\beta$ -phenylethyl acetate gives  $\beta$ -cyclohexylethyl alcohol,  $\text{C}_6\text{H}_{11}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ .

When cinnamaldehyde is reduced in the presence of palladous chloride and gum arabic in aqueous solution, the product is mainly phenylpropaldehyde; with acetic acid as solvent and with  $\text{PtCl}_4$  and gum arabic,  $\gamma$ -phenylpropyl alcohol is formed; and with more  $\text{PtCl}_4$ ,  $\gamma$ -cyclohexylpropyl alcohol.

**Hydrogen under High Pressures.**—*Ipattieff* (B., 1901-1912) was the first to study hydrogenation at pressures of 100-120 atmospheres with nickel and palladium in a special gun-metal bomb heated in an electric furnace at  $230^\circ$ - $260^\circ$ . The most efficient catalyst was  $\text{Ni}_2\text{O}_3$ , and only 2-3 gm. were required for 20-30 gm. of the substance to be reduced, and it can be used a second time. Under such conditions, acetone yields pure isopropyl-alcohol; acetylacetone, the glycol,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}_3$ ; phenol, hexahydrophenol; diphenyl, dicyclohexyl; naphthalene, tetra- or decahydro-naphthalene; dibenzyl, dicyclohexylethane;  $\alpha$ - and  $\beta$ -naphthols,  $\alpha$ - and  $\beta$ -decahydronaphthols, and similarly for sodium  $\beta$ -naph-

thioate; benzophenone, diphenylmethane; sodium benzoate, sodium hexahydrobenzoate (60 per cent yield) and aniline, diphenylamine, quinoline, anthracene, phenanthrene and acenaphthene, the corresponding compounds with fully hydrogenated benzene rings.

## B. Industrial Hydrogenation \*

Catalytic reduction is now used for the production of the following substances:

(1) Methanol and synthol. (2) Hydrocarbons. (3) Alcohols from fatty acids or glycerides. (4) Alcohols from aldehydes and ketones. (5) Hardened oils. (6) Hexahydrobenzene derivatives. (7) Tetralin and decalin. (8) Petrol and lubricating oils.

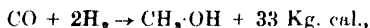
The methods used are largely based on the simple processes devised by *Sabatier*, *Willstätter* and *Ipatieff*, either in the gaseous or liquid phase. The temperature must be regulated as dissociation and polymerization products occur at higher temperatures, but on the whole rise of temperature favours hydrogenation. Increased pressure is often employed especially as the reactions are all accompanied by contraction of volume.

The catalysts are usually nickel or more rarely copper, nickel is the more active, but is more readily poisoned and is sometimes deposited on a carrier such as *Kieselguhr*, pumice or clay. Such catalysts are more durable and more heat resistant than the metal itself. Activated nickel turnings and wool are also used. The activation is accomplished by steeping in dilute hypochlorite solution or by electrolysis in a sodium carbonate solution, and then washing, drying and reducing at 250°. The method of preparation of the catalyst affects its activity, and as a rule those prepared at lower temperatures have the greater activity. Other factors are the amount of surface exposed, the nature of the surface and the crystal form. The tendency is to use a continuous process, the oil and hydrogen passing continuously over the catalyst. Small amounts of arsenic act as poisons to the catalyst, and hence the materials require purification before use. In the hydrogenation of oils the presence of free fatty acids and of protein

\* *Catalytic Processes in Applied Chemistry*, 2nd Edition. Hilditch and Hill, London, 1937.

is undesirable. The great bulk of the hydrogen used is manufactured by decomposition of steam, and water gas over  $\text{Fe}_3\text{O}_4$  and removing the carbon monoxide and dioxide (about 2 per cent), but each year larger proportions are made electrolytically, especially where cheap current is available.

**Methyl Alcohol—Methanol.**—The production of methanol from water gas or preferably water gas subjected to the catalytic hydrogen process ( $\text{CO} + \text{H}_2\text{O} \rightarrow \text{CO}_2 + \text{H}_2$ ) over oxide of iron so that the proportions of CO to  $\text{H}_2$  are roughly 1 : 2,



has largely replaced the older method of production from wood distillation products. It is employed in large quantities as a methylating agent in the dye industry, for use as a solvent, and also for manufacturing formaldehyde required in the synthetic resin (plastic) industry (Chap. LX, C.). The conditions of synthesis are: a catalyst of ZnO or preferably a basic zinc chromate (75 at. Zn to 25 of Cr), or chromium and manganese oxides at a temperature of about  $400^\circ$  and a pressure of 200 atmospheres. Sulphur compounds must not be present in the gases, and traces of Fe, Co or Ni in the catalyst tend to produce methane. The reaction is reversible and exothermic, the yield tends to diminish with rise in temperature, and temperature is regulated by an efficient system of heat exchangers, and as there is a volume decrease the yield tends to increase with rise of pressure. To prevent formation of methane the vessel is lined with copper, silver or aluminium, or alloys which do not yield carbonyls. Carbon dioxide can be reduced in a similar manner,  $\text{CO}_2 + 3\text{H}_2 \rightarrow \text{CH}_3\cdot\text{OH} + \text{H}_2\text{O}$ , and gaseous by-products obtained in certain fermentations can be used for the purpose (e.g. in formation of butyl alcohol).

By the addition of alkali to the catalyst and working at slightly higher temperatures the product is a complex of a small amount of hydrocarbons with large amounts of alcohols ( $\text{C}_4$  to  $\text{C}_7$ ), including 2-methyl-1-butanol, 2-methyl-1-pentanol, 2 : 4-dimethyl-3-pentanol, and other oxygen compounds probably formed by processes of dehydration from lower alcohols. The product is usually termed **Synthol**. According to *Morgan J. S. C. I.*, 1932, 1T), the best catalyst is a mixture of chromium and manganese oxides containing 15 per cent of rubidium oxide.



**Hydrocarbons.**—A mixture of hydrocarbons can be obtained from water gas ( $\text{CO} : \text{H}_2 = 1 : 2$ ) at atmospheric pressure by using a cobalt-thorium-Kieselguhr catalyst and temperatures of  $200^\circ$ . The product consists of 98 per cent of paraffins varying from methane to solids, and by fractionation can yield motor fuel, benzines, lubricating oils and waxes (*Fischer and Tropsch, 1926*).

**Hydrogenation of aldehydes and ketones** by passing hydrogen and the vapour of the compound over a heated nickel catalyst on pumice or Kieselguhr. Ethyl alcohol is manufactured by this process from aldehyde in Switzerland and isopropyl alcohol from acetone in America, as this alcohol is required in perfumery in place of ethyl alcohol. In the latter reaction the optimum temperature is  $150^\circ$ – $180^\circ$ , and proceeds best under pressure.

**Hardening of Fats.**—The process of greatest commercial importance is the hydrogenation of vegetable and fish oils and fats. As already stated (p. 183) the oils of the vegetable and animal kingdom are rich in glycerides of oleic, linolic and linolenic acids, and these on complete reduction yield tristearin. This hydrogenation is accompanied by a rise in the melting-point, a diminution in the iodine value, finally to zero, and a corresponding decrease in the value of the refractive index. The course of the reduction can be readily followed by determining the refractive index of samples from time to time. As a rule complete hydrogenation produces too hard a fat, but by partial hydrogenation it is possible to obtain fats of any consistency suitable for use as butter substitutes (margarine) or as tallow substitutes in the soap and candle industries. The process of hydrogenation is selective, i.e. the more unsaturated glycerides are first reduced, e.g. all linolein to olein before the latter is attacked. By reduction of linolein it is possible to obtain an iso-olein with the double linkage in a position different from what it is in ordinary olein; it has also been proved that during the reduction of olein itself isomeric change can occur and glycerides of elaidic and other isomeric oleic acids can be formed. This has a disadvantage in industry as the salts of these solid oleic acids have not the same lathering power as has sodium oleate and further the crystalline structure of the iso-oleins is different from that of the stearin and thus affects the consistency of the edible fat.

An activated nickel catalyst (p. 748) is generally used, and the process made continuous.

The oils most commonly used are: (a) Marine animal oils, e.g. body, liver and blubber oils. They are usually impure, highly coloured, contain much free fatty acids, and are used for making solid fats for soap manufacture. (b) Vegetable oils, e.g. cotton seed, soya bean, ground nut, &c. These are usually much purer, free from fatty acids, and yield solid edible oils of great purity suitable for use in margarine manufacture.

**Hydrogenation of Benzene Compounds.**—Each molecule of the benzene compound requires six atoms of hydrogen for complete reduction or one ton of phenol requires 25,000 c. ft. of hydrogen. The materials used are usually phenol, and the cresols in a form free from sulphur and tar. The catalyst is nickel, the temperature  $160^{\circ}$ – $200^{\circ}$ , usually under a pressure of 4 atmospheres and upwards, with sodium carbonate present as a promoter. The products, sextol, &c. (cf. p. 477), are used as solvents as also their acetyl derivatives. During the reduction of phenol, the  $\Delta^1$ -tetrahydrophenol is formed which passes over into the ketonic form, viz. ketocyclohexane or sextone. The reduction products boil some  $20^{\circ}$  lower than the original phenols.

**Hydrogenation of Naphthalene** takes place at  $170^{\circ}$ – $200^{\circ}$  under 10–15 atmospheres pressure, but great care has to be taken in the purification of the original hydrocarbon. The products tetrahydro-naphthalene, **tetralin**, b.-pt.  $206^{\circ}$ – $208^{\circ}$ , and decahydro-naphthalene, **decalin**, b.-pt.  $190^{\circ}$ – $191^{\circ}$ , are useful solvents. By similar processes menthol can be obtained by reducing thymol, and piperitone, a terpene ketone,

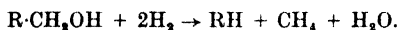
$$\begin{array}{c} \text{CMe} \diagup \text{CH} \cdot \text{CO} \\ \text{CH}_2 \cdot \text{CH}_2 \diagdown \end{array} \text{CH} \cdot \text{CHMe}_2$$
 present in oils from many species of eucalyptus, e.g. *E. dives* and *E. piperita* (Chap. LVII, B2), when reduced yields menthone and menthol.

**Formation of Alcohols from Fatty Acids and Glycerides.**—The conversion of an ester into the corresponding alcohol ( $\text{CO}_2\text{R} \rightarrow \text{CH}_2\cdot\text{OH}$ ) can be brought about catalytically using as catalyst a basic copper chromate ("copper chromate") at a temperature of  $200^{\circ}$  and a pressure of 150–200 atmospheres, or even at atmospheric pressure:



(Adkins and others, J. A. C. S., 1931, 1091, 1095; 1933, 1293).

If nickel replaces copper in the catalyst the reduction proceeds further, and the product is a saturated hydrocarbon:



By using a natural fat a mixture of higher alcohols is obtained which can be separated by careful fractionation under reduced pressure.

**Hydrogenation of Petroleum.**—This process is used in Canada and U.S.A. in the case of crude petroleum with high asphalt or high sulphur content, or even with refinery residues. A temperature of 500° and 3000 lb. pressure is used and the products are petrols, burning and lubricating oils.

For many years two different views have been held as to the mechanism of catalytic hydrogenation and similar processes. The one was a chemical theory postulating the formation of unstable compounds between the catalyst and the hydrogen, unstable metallic hydrides which could not be isolated but which induced hydrogenation. When it was shown that the compound reduced can undergo chemical change during hydrogenation, e.g. the change of oleic into *iso*-oleic acid (shifting of the double bond and stereochemical change), it became necessary to assume that the organic compound also entered into chemical action with the catalyst. *Sabatier* and *Maihle's* proof that different metallic oxides have different actions on ethyl alcohol, e.g. some dehydrogenate and others dehydrate (cf. this Chap., D.) supports the view that there is a chemical action between the catalyst and the compound undergoing change, and in certain cases it is possible to isolate intermediate compounds, e.g. ethyl hydrogen sulphate in the action of sulphuric acid on alcohol, and barium acetate in the catalytic formation of acetone from barium carbonate and acetic acid. This was supported by *Armstrong* and *Hilditch's* proof (P. R. S., 1919, **96**, A., 137; cf. *Maxted*, J. C. S., 1921, 225; 1936, 635) that in catalytic hydrogenation in a liquid phase equal amounts of the unsaturated compound are hydrogenated in unit time at any stage of the process, i.e. the reaction is of the nil-molecular order.

The other view, at first purely physical, was that the gas was adsorbed and enormously concentrated on the catalyst surface, and the change was a function of the rate of diffusion of the organic compound into this layer. It was subsequently found that certain gases are adsorbed to a much greater

extent than others, e.g.  $H_2$ ,  $C_2H_4$ ,  $CO$  as compared with  $N_2$  and  $He$ , and further that the former group give a much greater heat of adsorption than the latter, and such adsorption was termed "activated adsorption" and dealt with unimolecular layers. The heat evolved is of the order of a mild chemical reaction, and the forces involved are indistinguishable from what is termed chemical affinity; the formation of definite intermediate chemical compounds is probably rare in heterogeneous catalysis. High temperatures adversely affect a catalyst produced at lower temperatures, and in the case of nickel exposure to high temperatures produces a diminution in bulk of the catalyst and a corresponding loss of activity.

*Taylor* (P. R. S., 1925, A., 108, 105; J. A. C. S., 1931, 578) points out that hydrogenating catalysts prepared at low temperatures have, when examined by X-rays, a definite lattice structure of the crystalline material, but that probably local excrescences of irregular formation of atoms occur above the crystal surface, and these may be the seat of catalytic activity.\* Nickel with a Kieselguhr or charcoal support can withstand high temperature better than the unsupported metal; it appears to be protected in much the same manner as platinum or palladium by colloidal gum arabic.

**Catalyst Poisons.**—The poisoning of a catalyst may be due to several causes. In the case of hydrogen sulphide or acids some of the activated hydrogen atoms undergo chemical changes and become deactivated; in the case of resins, tars, &c., in colloidal suspension they are adsorbed and prevent the other interacting substances coming in contact with the catalyst. Similarly carbon monoxide is adsorbed in preference to hydrogen, and thus diminishes the reducing power of the catalyst.

Alkyl sulphides are more toxic than  $H_2S$ , and the toxicity increases with the alkyl group up to cetyl sulphide which is 34 times as toxic as  $H_2S$ .

Thiols are also toxic and dithiols less than the monothiols. Probably the S becomes anchored to a catalyst atom and the alkyl groups inhibit the approach of the reagents and lessen the effectiveness of the catalyst.

The presence of small amounts of a poison sometimes has a beneficial effect, especially when it is desired to slow down the reaction in order to isolate a particular product. Thus in

\* For other views cf. Hilditch and Hill, Chap. II.

the reduction of benzoyl chloride in pure benzene with the aid of colloidal palladium little or no benzaldehyde can be obtained, whereas by using commercial benzene (containing the sulphur compound thiophene) good yields can be obtained—also by supporting the catalyst on barium sulphate (*Rosemund* and others, B., 1921, 425, 638, 1092, 2033, 2038). The presence of water is sometimes desirable, e.g. with a copper catalyst in the oxidation of methyl alcohol to formaldehyde, the dehydrogenation of ethyl alcohol to acetaldehyde and with a nickel catalyst in the hydrogenation of acetaldehyde to ethyl alcohol.

**Catalyst Stimulants.**—The addition of a small amount of a second solid sometimes increases the activity and the stability of a catalyst. The addendum may be another metal; thus *Ipatieff* (B., 1910, 3387) proved that the presence of a little iron improved the catalytic activity of copper in hydrogenations; the two metals must be intimately mixed, e.g. the oxides precipitated together and then reduced. A very common phenomenon is the increased activity produced by the addition of an oxide to a metal. Thus 1–2 per cent of alumina or silica precipitated with the nickel increases the absorptive power and activity of the metal. Similarly nickel supported on activated charcoal, Kieselguhr or diatomaceous earths is more active than the unsupported metal, whereas on ordinary charcoal, fuller's earth or pumice the activity is unaffected.

Alkali oxides or carbonates are often beneficial, e.g. the presence of  $\text{Na}_2\text{CO}_3$  (as much as 25 per cent) in the nickel used for hydrogenating liquid phenols to cyclohexanols.

A mixed oxide is frequently a more efficient catalyst than either component. Thus zinc oxide can be used for obtaining methanol from water gas, but  $\text{ZnO} + \text{Cr}_2\text{O}_3$  is more efficient. Copper chromite ( $\text{CuO} + \text{Cr}_2\text{O}_3$ ), obtained by reducing basic copper chromate, is very useful in reducing higher aliphatic acids or esters to the corresponding alcohols (*Adkins* and *Connor*, J. A. C. S., 1931, 1095), as 90 per cent yields can be obtained. At higher temperatures saturated hydrocarbons are formed, either under pressure or at atmospheric pressure using a silica gel support:



Copper chromite can be used in most cases in place of nickel for hydrogenating carbon compounds; zinc chromite on the

other hand hydrogenates carbonyl (C:O) compounds but not olefines (C:C) (*ibid.* 3719), thus oleic acid and hydrogen with Ni give stearic acid, whereas with zinc chromite they give the unsaturated alcohol  $\text{CH}_3(\text{CH}_2)_7\text{CH}:\text{CH}(\text{CH}_2)_7\text{CH}_2\text{OH}$  (*ibid.* 1937, 1).

**Selectivity.**—In mixtures it is found that monosubstituted olefines are more readily reduced than di, di than tri, and tri than tetra. Butadienes are also reduced more readily than olefines (J. C. S., 1928, 823, 2190; 1933, 687), but it is by no means universally true that in a mixture of two compounds the order of preferential reduction runs parallel with the relative speeds of reduction of the pure compounds, as in mixtures of allyl alcohol and  $\Delta^2$ -hexenoic acid or of pinene and cinnamic acid the component which is reduced more slowly when taken separately is preferentially reduced in the binary mixture. In a mixture of oleic and erucic acids both are reduced at practically the same rate.

At 125°–175° and 125–200 atm. the relative rates of hydrogenation of the individual compounds follow the decreasing order: quinoline, benzene, toluene, phenol, benzyl alcohol, pyridine, diphenylamine, acetanilide, aniline, whereas in binary mixtures it is found that amino-compounds inhibit the reduction of benzene or toluene, whereas the latter accelerate that of aniline (*Adkins and Diwoky*, J. A. C. S., 1931, 1868).

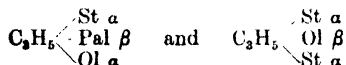
For hydrogenation of conjugated dienes cf. Chap. LI, C2.

On the whole nickel is more selective than the noble metals and the main addition is to the 3 : 4-position in a butadiene-carboxylic acid. Similar differences are met with in hardening oils, with platinum the reduction is usually complete, but with nickel the reaction is easily stopped at the formation of oleates from the more highly unsaturated glycerides, but at high pressures and lower temperatures the behaviour of nickel is somewhat similar to that of platinum (cf. *Harper*, J. S. C. I., 1937, 308T).

With acetylenes there are always two distinct stages, and the speeds of the two stages vary considerably with the nature of the substituents in the original acetylenes.

The reduction of triolein to tristearin proceeds in three distinct stages which proceed in diminishing rates so that large amounts of steardiolein are formed before any appreciable amounts of tristearin are noticeable. With a mixture

of palmito-stearo-olein and distearo-olein the former is hydrogenated almost exclusively in preference to the latter, so that tristearin is not formed in any quantity until all the glycerides containing the palmyl group have become fully reduced. This may be due to the fact that the palmyl group is in the  $\beta$ -position, whereas the stearyl is in the  $\alpha$ -position, i.e.



### C. Oxidation and Dehydrogenation

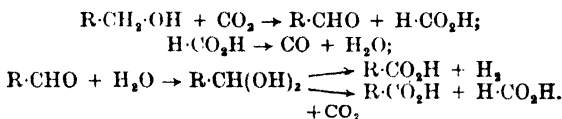
The addition of oxygen or the withdrawal of hydrogen both fall under the term oxidation, but the latter is more commonly termed *dehydrogenation*. Both reactions can be catalysed.

**Oxidations.**—Oxidation of organic compounds with atmospheric oxygen can often be accomplished in the presence of a suitable catalyst. Among such oxidations of technical importance are the production of phthalic anhydride from naphthalene, anthraquinone from anthracene, maleic anhydride from benzene. The important points in these cases are: (1) Proportions of air and carbon compound, (2) Temperature control, particularly as the reactions are exothermic, and (3) Type of catalyst. The common catalyst is  $\text{V}_2\text{O}_5$ , and temperature  $350^\circ\text{--}400^\circ$ .  $\text{Mo}_2\text{O}_3$  is not so active, and platinum too active, as it tends to bring about complete oxidation, e.g. benzene to carbonic anhydride. Vanadium pentoxide deposited on a zeolite has been recommended with the addition of an alkali sulphate as a stabilizer. A lower temperature, viz.  $250^\circ\text{--}300^\circ$ , can be used with tin vanadate as catalyst (*Maxted*, J. S. C. I., 1928, 101T). Other oxidations are toluene to benzoic acid and nitro-, bromo- and chloro-toluenes to the corresponding benzoic acids (yields poor).

The greater part of formaldehyde (formalin) required in the chemical industry is manufactured by the catalytic oxidation of synthetic methanol using a fine metal gauze (silver, silver-copper alloy or usually copper) as catalyst. The length of gauze is restricted to 70–120 mm. in order to avoid further oxidation to formic acid or carbonic anhydride, with a ratio of oxygen to methanol of 0.315 : 1 (by vol.) and a temperature of  $450^\circ$ . The composition of the reacting vapour is controlled

by passing air at a constant rate through methyl alcohol heated to 40°-50°. Ordinarily the 40 per cent formaldehyde solution is obtained, but by using anhydrous methanol the product is a 60 per cent solution.

Carbonic anhydride can oxidize certain primary alcohols to aldehydes and acids in the presence of  $U_3O_8$ ,  $MoO_3$  and pumice,  $Sn(VO_3)_2$  or  $MoO_3 + V_2O_5$  at temperatures of 400°-450°. The relative yields of aldehyde and acid vary with the catalyst. Using isoamyl alcohol and  $U_3O_8$  the relative proportions of aldehyde and acid are 72.9 and 12.3 per cent, but with  $MoO_3 + V_2O_5$  and pumice 40.8 and 37.9 per cent. Benzyl alcohol gives 54 per cent aldehyde and 32.5 per cent acid with  $MoO_3$  at 400°. The reaction is represented as follows:



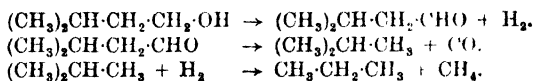
**Dehydrogenation.**—The dehydrogenation of primary alcohols into aldehydes and hydrogen takes place when the vapour is passed through a tube containing iron, zinc, brass, zinc oxide, ferric oxide, or stannic oxide. The method usually adopted is to use metallic copper obtained by reducing the granular fused oxide and a temperature of 300°. As the reaction is endothermic the vapour of the alcohol is raised to about 300° before entering the reducing chamber. The aldehyde or ketone and unoxidized alcohol are separated by passing through fractionating columns. The gaseous products are hydrogen with 1 to 2 per cent of carbon mon- and di-oxide. With ethyl alcohol and copper at 300° practically no side reactions occur, but only 25 per cent of the alcohol used is dehydrogenated, but the 75 per cent recovered can be passed over the catalyst again and ultimately a 90-92 per cent yield of alcohol obtained. When nickel is used the side reactions, accompanied by formation of oxides of carbon, are more marked.

Iso-butyl alcohol (methyl-ethyl-carbinol) gives methyl ethyl ketone and *n*-butyl alcohol gives *n*-butaldehyde. Cyclohexanol yields cyclohexanone, borneol yields camphor, and ketonic alcohols yield diketones (Bull. Soc., 1908, [IV], 3, 119).

The reactions: Primary alcohol  $\rightleftharpoons$  aldehyde +  $H_2$ , secon-

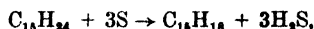


dary alcohol  $\rightleftharpoons$  ketone +  $H_2$ , are reversible in the presence of the catalyst, and the yield of aldehyde and ketone will vary with (a) temperature, (b) pressure, and (c) catalyst. When alcohols are heated with hydrogen under pressure, and in contact with zinc or iron, the final products consist mainly of hydrocarbons if the temperature is fairly high, e.g. isoamyl alcohol yields considerable amounts of propane and methane. The formation of these latter is probably due to the following series of reactions:



The process of dehydrogenation \* has been utilized in the elucidation of the structure of complex natural products, more especially in the sesquiterpene, sterol and bile acid compounds (cf. Chap. LXII, A. and B.). The dehydrogenations are usually brought about in the presence of sulphur (*Curie*, 1874), selenium (*Diels*, 1927), or metals such as platinum, palladium or nickel (*Zelinsky*, 1911), particularly the two former and usually on an inert carrier such as charcoal or asbestos.

The reactions with sulphur and selenium are similar and the hydrogen eliminated is removed as  $H_2S$  or  $H_2Se$ . The reactions are not catalytic and the amount taken is that theoretically required; thus for the dehydrogenation of a sesquiterpene it is given by the equation



and as a rule a solvent is not used. With the metals the reaction is catalytic and hydrogen is evolved as such or can be used up in hydrogenating part of the material. The temperature used in the case of sulphur is  $180^\circ$ – $250^\circ$ , with selenium  $280^\circ$ – $350^\circ$ , and noble metals  $300^\circ$ . In many cases selenium gives better yields than sulphur and can be used in cases where sulphur gives negative results.

The uses of dehydrogenation in the study of structure is based on the generalization that during dehydrogenation the ring skeleton remains intact, and hence the nature of the aromatic product formed gives the structure of the rings present in the original compound. The correctness of this generalization has been proved by the dehydrogenation of

\* For summary cf. *Linstead*, Rep., 1936, 294.

partially or completely reduced aromatic compounds. Thus tetralin and sulphur gives a 70 per cent yield of naphthalene; limonene yields *p*-cymene (15 per cent), and terpinene, where both double links are cyclic, gives 50 per cent of *p*-cymene.

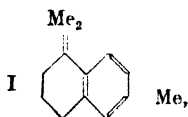
With both sulphur and selenium fully reduced rings resist hydrogenation; thus 1- (1'-naphthyl) *cyclohexene* is readily dehydrogenated to phenylnaphthalene, whereas the corresponding 1-naphthyl-*cyclohexane* is not (J. C. S., 1936, 1431). Similarly alkyl substituted decalins are not dehydrogenated at 320°-330°, whereas the corresponding octalins readily yield alkylnaphthalenes. Trans-decalin can, however, be dehydrogenated at a temperature of 370°-390° with selenium. Similar resistance is met with in the case of cholestane (Chap. LXII, A.) and perhydrophenanthrene, but a bicyclic system with one aromatic and one completely reduced ring is often hydrogenated, e.g. 2-cyclohexylnaphthalene.

When platinum or palladium is used a completely reduced ring compound can be dehydrogenated, e.g. *cyclohexane* derivatives give the corresponding benzene compounds, decalin gives naphthalene and hexahydrofluorene gives fluorene. On the other hand *cyclo-pentane* or -pentene compounds resist dehydrogenation with these metals. Under similar conditions a partially reduced benzene derivative yields a mixture of the true aromatic compound and of the fully reduced compound; thus *cyclohexene* and *cyclohexadienes* yield mixtures of benzene and *cyclohexane*, and cyclic terpenes behave in the same manner (Zelinsky and others, B., 1924, 1066, 2055; 1925, 185, 864; 1933, 1420).

Ring substituents, e.g. alkyl—except complex chains—methoxy and even  $\text{CO}_2\text{Et}$  often remain intact during dehydrogenation, so that the process is not only of value for determining the ring skeleton of the compound but also for the positions of certain substituents, e.g. most sesquiterpenes yield cadalene (1 : 7-dimethyl-4-isopropyl naphthalene) or eudalene (6-methyl-4-isopropyl naphthalene), thus fixing the positions of the substituents in the original hydrocarbons (Chap. LVII, F.).

Even carboxylic groups can be retained in hydro-naphthalenes and phenanthrenes by working under reduced pressure; an exception is 1-methyltetralin-4-carboxylic acid, where  $\text{CO}_2$  is eliminated and 1-methyl-naphthalene is formed (C. R., 1934, 199, 1131).

During dehydrogenation a methyl group may be eliminated, when sulphur is used, as methyl sulphide. The simplest example is met with in ionene (I), which yields 1:6-dimethyl naphthalene. The methyl group eliminated is one of the



quaternary ones, i.e. one in the group  $\begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \text{CMe}_2$ . Similar com-

pounds, e.g. 1:2-dimethylcyclohexane are difficult or impossible to dehydrogenate when metal catalysts are used (cf. also *Clemo* and *Dickenson*, J. C. S., 1937, 255). On the other hand all three methods tend to eliminate quaternary methyl groups when they are in an angular position, i.e. attached to a carbon atom common to two rings. This elimination was observed by *Ruzicka* in the case of the sesquiterpene, selinene, and the corresponding alcohol eudesmol. This is a reaction of great interest, and when it is observed that a natural product loses a methyl group during dehydrogenation the conclusion is usually drawn that the methyl group occupies an angular position (cf. *Abietic Acid*, Chap. XXXII, B3, and *Sterols*, Chap. LXII, A.).

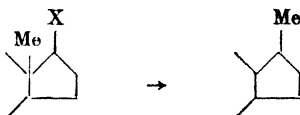
Similarly an angular  $\cdot\text{CO}_2\text{Et}$  group is removed during dehydrogenation.

Certain so-called abnormal reactions occur during dehydrogenation, but usually at higher temperatures than those stated on p. 758. It follows that a structural formula for a complex compound based on dehydrogenations carried out at temperatures of  $370^\circ$ – $400^\circ$  must be accepted with caution.

At these higher temperatures the following reactions have been noted:

- (1) A ring methoxy group may be completely eliminated.
- (2) Alkyl groups may wander during dehydrogenation, e.g. from the 4- to the 1-position in the naphthalene ring, but never from the 1- to 2-position in naphthalene or from 3- to 4-position in phenanthrene derivatives (*Helv.*, 1936, 386). Several suspected cases of migration have been shown to be cases of wandering during the synthesis of the compound and not

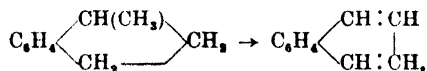
during its dehydrogenation. A migration of a methyl group can occur when a neighbouring substituent, e.g. hydroxyl, is eliminated, the methyl taking the place of the eliminated group. A wandering of an angular methyl group also occurs during dehydrogenation in the sterol group (Chap. LXII, A.), the Me taking the place of a complex carbon chain X which is eliminated.



(3) Unsaturated side chains, e.g. allyl, may be hydrogenated even at the lower temperatures (Cook and others, J. C. S., 1935, 767, 1633), and even cyclic double links can be reduced; thus 1-naphthyl-*cyclo*-hexene yields a mixture of phenyl- and *cyclo*-hexyl-naphthalenes. With certain compounds only partial dehydrogenation occurs, e.g. dodecahydrochrysene.

(4) *Change in ring structure.*

(a) *Ring enlargement* from 5 to 6 carbon rings.  $\alpha$ - and  $\beta$ -methylhydrindenes with selenium at 450° yield naphthalene:



and hydrindenes with larger alkyl groups yield naphthalene and not alkyl-naphthalenes.

Also sterols and bile acids at high temperature yield chrysene, although at lower temperatures the product is *Diels'* hydrocarbon,  $\text{C}_{18}\text{H}_{16}$ , containing a *cyclo*-pentene ring in place of one of the 6 C rings of chrysene. Similar changes occur when metals are used (cf. Sterols).

(b) *Decrease in size of ring.* When *cyclo*-heptane and *cyclo*-octane are heated with selenium at 440° the products are respectively toluene and *p*-xylene.

(c) *Formation of new ring.* 1:2-Diethylcyclohexene and selenium at 420° yield naphthalene, and somewhat analogous is the formation of phenanthrene by heating di-*o*-tolyl with sulphur at 250°, or dibenzyl with platinized carbon (J. S. C. I., 1936, 347T)

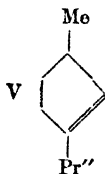
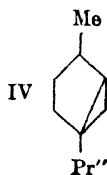
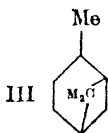
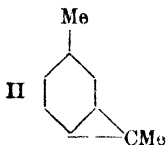
Small yields of aromatic hydrocarbons are formed by the dehydrogenation of various aliphatic hydrocarbons with

platinized charcoal at 300°–310°, e.g. di-isobutyl yields *p*-xylene and di-isoamyl yields *m*-cymene (B., 1936, 1862).

(d) *Complex ring changes.* The *spiro* compound I when heated with selenium at 280°–320° yields naphthalene, and 1-*cyclo*-pentyl-hydrindene by sulphur dehydrogenation yields phenanthrene (Robinson, J. C. S., 1936, 80).



With the bicyclic terpenes and metals the tri or tetra ring is ruptured, and the product in the case of carane II and pinane III is the aromatic hydrocarbon *p*-cymene. With thujane IV the tri ring is ruptured and the product is an isomeric stable pentene V which does not undergo dehydrogenation.



**Oxygenated Compounds.**—If the ring contains a carbonyl group the oxygen is often eliminated, but occasionally yields a phenol, e.g. 7-methyl-1-tetralone yields 7-methyl-1-naphthol. As already stated, methoxy groups frequently remain intact.

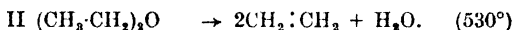
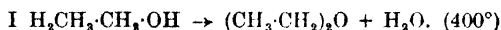
Acid anhydrides, e.g. naphthalene-2:3-dicarboxylic anhydride with selenium and a hydrogen donor (*p*-cyclohexyl-phenol) yields 2:3-dimethyl-naphthalene, whereas the isomeric 1:8-anhydride yields 1-methylnaphthalene, the second CO group being eliminated.

The differences observed between dehydrogenation with sulphur and selenium (chemical) on the one hand and dehydrogenation with the aid of metal (catalytic) may be due

to the addition of S or Se to an unsaturated centre followed by the elimination of  $\text{H}_2\text{S}$  or  $\text{H}_2\text{Se}$  in the chemical process and to the activation of hydrogen by the metal, followed by the elimination of this hydrogen as such, or its addition to an unsaturated centre (not an aromatic centre) in the same or even in a neighbouring molecule.

### D. Dehydration

The dehydration of an alcohol to an ether or to an olefine can be effected catalytically by using a suitable oxide catalyst, e.g.  $\text{Al}_2\text{O}_3$ .



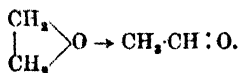
The formation of ether or olefine depends upon the nature of the alcohol, on the temperature and on the catalyst. On the whole tertiary alcohols lose water most readily, a lower temperature favours ether formation, as also does increased pressure. The activity of a given oxide catalyst varies with its mode of formation and its activity is always diminished by strongly heating. Of the various oxides examined the most efficient appear to be thoria and alumina.

Aluminium phosphate,  $\text{AlPO}_4$ , is also used.

With *n*-butyl alcohol the product is a mixture of  $\alpha$ -butylene,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}:\text{CH}_2$ , 73 per cent, and *isobutylene*,  $(\text{CH}_3)_2\text{C}:\text{CH}_2$ , 27 per cent at  $32^\circ$ , but with *isobutyl* alcohol at  $310^\circ$  the proportions are 31.5 of  $\alpha$  and 68.5 of *iso* (*Senderens*, Bull. Soc., 1907, [IV], 1, 692).

Dehydration does not occur in the absence of the catalyst, even when higher temperatures are used. Reaction I is reversible, as ether and water, under similar conditions, yields a certain amount of alcohol.

Unsaturated hydrocarbons can also be obtained by the action of aluminium oxide on cyclic alcohols; thus menthol (Chap. LVII, B2) yields menthene. The same catalyst at  $200^\circ$ – $300^\circ$  is able to transform ethylene oxide and its homologues into the isomeric aldehydes:



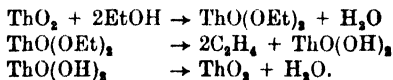
A similar change occurs in the absence of the catalyst, but at a higher temperature, viz.  $500^{\circ}$ – $600^{\circ}$ .

Numerous other substances, e.g. pumice, animal charcoal, sand, red phosphorus, and aluminium phosphate, can decompose alcohols into olefines and water, but oxide of aluminium appears to be the best (*Senderens*, C. R., 1907, **144**, 381, 1109). *Bouveault* has designed a special apparatus for the preparation of olefines by this method.

The action of silica as a catalytic agent is extremely characteristic. Pure precipitated silica, moderately calcined, decomposes ethyl alcohol at  $280^{\circ}$ , yielding pure ethylene. After it has been more strongly calcined, it induces decomposition only at a higher temperature, and then yields ethylene and water together with hydrogen and aldehyde. Pulverized quartz can yield as much as 50 per cent of the theoretical amount of hydrogen and 50 per cent of ethylene. Similarly, alumina which has been strongly calcined decomposes part of the alcohol into hydrogen and aldehyde. Experiments made with gypsum ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ) dehydrated below  $400^{\circ}$  and with anhydrite ( $\text{CaSO}_4$ ) indicate that the catalytic dehydration of alcohols is effected by substances which are capable of forming temporary hydrates. Thoroughly calcined gypsum or natural anhydrite decomposes alcohol at high temperatures only, and then yields mainly hydrogen and acetaldehyde; on the other hand, gypsum which has been dehydrated at a moderate temperature is capable of combining with water, and decomposes alcohol at about  $400^{\circ}$ , yielding ethylene (*Senderens*, *Annales*, 1912, **25**, 449).

*Sabatier* and *Maihle* (*Annales*, 1910 [viii], **20**, 289) have studied the action of the following metallic oxides on primary alcohols, e.g. ethanol:  $\text{ThO}_2$ ,  $\text{Al}_2\text{O}_3$ ,  $\text{W}_2\text{O}_5$ ,  $\text{Cr}_2\text{O}_3$ ,  $\text{SiO}_2$ ,  $\text{TiO}_2$ ,  $\text{BeO}$ ,  $\text{ZrO}_2$ ,  $\text{UO}_2$ ,  $\text{Mo}_2\text{O}_5$ ,  $\text{Fe}_2\text{O}_3$ ,  $\text{V}_2\text{O}_5$ ,  $\text{ZnO}$ ,  $\text{MnO}$ ,  $\text{CdO}$ ,  $\text{Mn}_3\text{O}_4$ ,  $\text{MgO}$ . The first four act almost entirely as dehydrating agents, and at  $340^{\circ}$ – $350^{\circ}$  give 90–100 per cent yields of olefine and little or no hydrogen (cf. *Baskerville*, J. A. C. S., 1913, 93). On the other hand, the last five oxides bring about dehydrogenation, and give practically 100 per cent of hydrogen and no olefine.  $\text{BeO}$  and  $\text{ZrO}_2$  give approximately equal volumes of hydrogen and olefine, i.e. they are mixed catalysers, as are practically all the intermediate oxides. For summary of actions in case of ethyl alcohol cf. *Morris*, *Chem. Rev.*, 1932, 465.

The mechanism of catalytic dehydration does not consist in the formation of unstable hydrates of the catalyst as at first supposed, but in the formation of alkyl salts, e.g. ethyl thorate or ethyl aluminate formed by the union of the alcohol with the acidic oxide used as a catalyst:



The reaction can be utilized for obtaining iso- from *n*-butyl alcohol. The latter dehydrogenated yields  $\Delta^1$ -butylene, and this with sulphuric acid and subsequent hydrolysis gives the iso-alcohol, methylethylcarbinol.

Ether can readily be prepared from absolute ethyl alcohol by passing over carefully dehydrated alum at about 200° and carefully fractionating the product. Higher ethers, e.g. *n*-butyl, are formed by passing the alcohol vapour over aluminium or chromium sulphate at temperatures below 300° and pressures up to 100 atmospheres.

Mixed and true aromatic oxides or ethers can be readily prepared by using  $\text{ThO}_2$  (C. R., 1914, 158, 608). For catalytic formation of hydrocarbons cf. *Senderens* and *Murat*, *Annales*, 1915 [ix], 4, 253.

## E. Esterification

*Sabatier* and *Maihle* (C. R., 1911, 152, 494) have shown that  $\text{TiO}_2$  is a good catalyst for the conversion of acids and alcohols into esters. The method is to allow a mixture of molecular proportions of the vapour of the two compounds to pass over a column of the dioxide kept at 290°–300°. The yield of ester is about 70 per cent, and the process is extremely rapid. A similar method may be used for hydrolysing esters, e.g. allowing a mixture of the ester vapour with an excess of steam to pass over the dioxide at 280°–300°. Similar results are obtained with thorium oxide, provided aromatic acids are used, and glucinum oxide behaves similarly.



## F. Amines, Nitriles, Thiols and Ketones

**Formation of Amines, Nitriles, Thiols.**—Amines are formed when a mixture of an alcohol and ammonia is passed over thorium dioxide at 350°–370° (C. R., 1909, **148**, 898; Bull. Soc., 1914 [iv], **15**, 327), a good yield of cyclohexylamine is obtained from the alcohol and ammonia over nickel at 150°, and the secondary amine almost exclusively at 190° (C. R., 1929, **189**, 927); thiols (mercaptans) are formed when a mixture of alcohol and hydrogen sulphide is passed over the dioxide at 300°–360° (C. R., 1910, **150**, 1217, 1569). The yields are especially good with primary alcohols, and even phenol gives a 17 per cent yield of thiophenol at 430°–480°; and metallic sulphides, especially CdS, at 320°–330°, decompose thiols into alkyl sulphides and hydrogen sulphide. Nitriles are formed when aliphatic acids and ammonia are passed over  $\text{Al}_2\text{O}_3$  or  $\text{ThO}_2$  at 500° (*Epps and Reid*, J. A. C. S., 1916, 2128). They are also formed when secondary and tertiary aliphatic amines are passed over nickel at 350°–380° (*Maihle*, C. R., 1917, **165**, 557; 1918, **166**, 996), hydrogen and unsaturated hydrocarbons being formed at the same time, or when esters and ammonia or aldehydes and ammonia are passed over  $\text{ThO}_2$  at 420°–440° (*ibid.* 1918, **166**, 121, 215).

**Ketones.**—Ketones can be prepared by the action of acid anhydrides or acids on thorium dioxide at 400°:



Simple and mixed aliphatic ketones and mixed aromatic aliphatic ketones have been prepared, the mixed ketones by using mixtures of two acids. Aromatic acids containing the carboxylic group attached to the benzene nucleus do not react unless mixed with an aliphatic acid, but acids of the type of phenylacetic do. The reaction probably consists in the formation of a salt and its subsequent decomposition into ketone, carbon dioxide and water (*Senderens*, Annales, 1913, **28**, 243; *Pickard and Kenyon*, J. C. S., 1913, 1923). Calcium or barium carbonate at 450°–500° can also be used in the case of acetic acid (*Squibb*, J. A. C. S., 1895, 187). When mixed acid vapours are passed over  $\text{Fe}_2\text{O}_3$  at 470°–480°, ketones are formed, more particularly from acids of the type of phenylacetic and

cinnamic acids (*Maille*, Bull. Soc., 1914, **15**, 324). Manganous oxide, MnO, also gives good results, e.g. 70 per cent yields. By this process adipic acid gives cyclopentanone (C. R., 1914, **158**, 830, 985). This oxide is of use for the preparation of acetone, as even dilute (20 per cent) solutions of acetic acid passed over MnO at 350° give theoretical yields of acetone (*Sidgwick and Lambert*, 1915).

A mixture of an acid with an excess of formic acid passed over TiO<sub>2</sub> at 250°–300° yields the aldehyde, with the exception of acids of the benzoic type, and even better results are obtained with MnO (*Sabatier and Maille*, C. R., 1912, **154**, 561; 1914, **158**, 985).

Formic acid behaves somewhat differently from the other fatty acids (*Sabatier and Maille*, C. R., 1911, **152**, 1212). Finely-divided Pd, Pt, Ni, Cu, Cd, and ZnO or SnO decompose it into carbon dioxide and hydrogen. TiO<sub>2</sub> and W<sub>2</sub>O<sub>5</sub> yield water, and carbon monoxide, and SiO<sub>2</sub>, ZrO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, &c., give both reactions.

A study of the synthetical value of acetylene in the presence of finely-divided metallic oxides has been made by *Tschitschibabin* (J. russ., 1915, **47**, 703). Acetylene and ammonia over heated Al<sub>2</sub>O<sub>3</sub>, Fe<sub>2</sub>O<sub>3</sub>, or Cr<sub>2</sub>O<sub>3</sub> at 300° yield pyridine bases, mainly  $\alpha$ - and  $\gamma$ -picolines (p. 686) and 2-methyl-3-ethylpyridine, together with pyrrole and piperidine bases. Acetylene and hydrogen sulphide over Al<sub>2</sub>O<sub>3</sub> give thiophene, and the method is recommended as a commercial one. Similarly acetylene and water over Al<sub>2</sub>O<sub>3</sub> at 400°–425° yield furane.

## G. Other Catalysts

**Iodine.**—The use of small amounts of iodine as a catalyst in the chlorination of acetic acid or the bromination of benzene (Chap. XIX, B.) has long been recognized. *Knoevenagel* (J. pr., 1914, **89**, 1) finds that small amounts of iodine accelerate many reactions and lead to the formation of purer products. This is especially noticeable in (a) the formation of thiodylarylamines from sulphur and diarylamine, the presence of 0.05 to 0.2 per cent of iodine producing a marked effect; (b) the condensation of aromatic amines with naphthols or naphthylamines; (c) the alkylation of primary aromatic amines, especially aniline and  $\alpha$ -naphthylamine, by the direct action of alcohols;

(d) the condensation of aromatic alcohols with ketones. Minute quantities of iodine are of value in obtaining unsaturated compounds by heating hydroxy compounds, e.g. unsaturated hydrocarbons from alcohols, particularly tertiary and some secondary, unsaturated ketones from ketonic alcohols, and unsaturated aldehydes from aldols. The reagent is also of value in condensing glycols to polyglycols (*Hibbert*, J. A. C. S., 1915, 1748), or in reactions involving elimination of hydrogen chloride (*Desai*, J. I. I. S., 1924, 235).

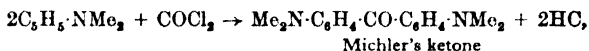
**Aluminium chloride.**—In the *Friedel-Crafts* reaction (pp. 405, 495) for the synthesis of aromatic hydrocarbons, ketones and di- and triphenyl-methane derivatives, aluminium chloride or an analogous metallic chloride is used as the condensing or catalytic agent. The amount of metallic chloride required varies considerably with the constitution of the reacting acid chloride and hydrocarbon. In some cases traces are sufficient, in others a molecular proportion or more is essential, in order to obtain good yields, e.g. in the preparation of ketones, and it is possible that the ketone as formed combines with the  $\text{AlCl}_3$ , thus removing it from the sphere of action. Aluminium chloride and analogous chlorides form well-defined additive compounds, not only with acyl chlorides but also with numerous other organic compounds, including hydrocarbons, e.g.  $3\text{C}_6\text{H}_6$ ,  $\text{AlCl}_3$  and ketones, Ket,  $\text{AlCl}_3$  (*Menschutkin*, Abs., 1909, i, 897; 1911, i, 273, 532; 1912, i, 100; ii, 922; *Perrier*, B., 1900, 815; *Steele*, J. C. S., 1903, 1470), and it is possible that the additive compounds are the reactive reagents (*Boeseken*, Abs., 1910, i, 152; 1911, i, 173), but often the reactive acyl or alkyl halogen compounds are not those which readily yield additive compounds with metallic chlorides, and the effect of the latter appears to be to produce a loosening of the halogen in the organic compound (Rec. trav., 1913, 1).

*Dougherty* (J. A. C. S., 1929, 576) finds that aluminium chloride with a mixture of two halogen compounds induces partial exchange of halogens. Thus  $\text{AlCl}_3$  with  $\text{MeCl} + \text{EtBr}$  gives a mixture of the four compounds,  $\text{MeCl}$ ,  $\text{MeBr}$ ,  $\text{EtCl}$  and  $\text{EtBr}$ , also  $\text{C}_2\text{H}_4\text{ClBr}$  gives a mixture of  $\text{C}_2\text{H}_4\text{Cl}_2$ ,  $\text{C}_2\text{H}_4\text{Br}_2$  and  $\text{C}_2\text{H}_4\text{ClBr}$ .

The activity of  $\text{AlCl}_3$  is diminished by the presence of adsorbed hydrogen chloride, which is very difficult to remove, but enhanced by the addition of ferric chloride, although this alone is less active than the aluminium compound (cf. Can.

J. Res., 1929, 400; 1930, 31; J. A. C. S., 1930, 4365; 1932, 290; 1935, 2584).

The aluminium chloride catalytic process is used industrially in the following cases: (1) Manufacture of toluene from benzene and methyl chloride. (2) Production of compounds of the type of *o*-benzoylbenzoic acid (Chap. XXVIII) from aromatic hydrocarbons, benzene, naphthalene, and their substituted derivatives. These acids are of importance as they readily undergo ring closure by loss of water, yielding anthraquinone and other more complex quinones. (3) By using carbonyl chloride and tertiary amines ketones of value in the dye industry can be prepared:



and this in its turn with another molecule of amine yields crystal violet (a triphenylmethane dye, Chap. XXX, A2).

Phenols and arylamines react with  $CO_2$  in the presence of  $AlCl_3$ ,  $FeCl_3$ , or  $ZnCl_2$  at  $100^\circ$ – $200^\circ$  and 40–150 atmospheres pressure; thus salicylic acid and  $CO_2$  yield 4:4'-dihydroxy benzophenone at  $105^\circ$ – $110^\circ$  and 70 atmospheres, or diphenyl ether at  $200^\circ$  and 120 atmospheres.

Dimethylaniline gives *p*-dimethylamino-benzoic acid (*Morgan and Pratt*, C. and I., 1931, 104).

Olefines can be used in place of alkyl chlorides in the *Friedel-Crafts* synthesis (J. A. C. S., 1927, 3142, 3150, 3157). The reaction proceeds very readily, and it is difficult to regulate the reaction so as to obtain a given product; as a rule the product is a mixture of mono-, di-, and much tri-ethylbenzene.

For use of  $AlCl_3$  mixed with  $CuCl$  for synthesis of aromatic aldehydes see *Gattermann Reaction*, p. 492.

The dynamics of the reaction have been investigated. In the benzylation of anisole in the presence of  $SnCl_4$  or  $AlCl_3$ , the velocity is proportional to the concentration of the catalyst (*Zeit. phys.*, 1904, 48, 424).

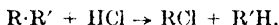
By a study of the reaction between *p*-bromobenzene-sulphonyl chloride and benzene in the presence of  $AlCl_3$ , *Olivier* (*Rec. trav.*, 1914, 91) draws the following conclusions: (1) The acyl chloride reacts solely in the form of the additive compound with  $AlCl_3$ . (2) One molecule of  $AlCl_3$  cannot transform more than one molecule of the acyl chloride. (3) The reaction is unimolecular with respect to the additive com-

pound. (4) In the absence of excess of  $\text{AlCl}_3$  the velocity constant is proportional to the concentration of the  $\text{AlCl}_3$ , when  $k$  is calculated for the compound  $\text{C}_6\text{H}_4\text{Br}\cdot\text{SO}_2\text{Cl}$ ,  $\text{AlCl}_3$ . (5) The velocity is greatly increased by an excess of  $\text{AlCl}_3$ . These facts point to the conclusion that the acyl chloride is activated proportionally to the concentration of the combined  $\text{AlCl}_3$  (cf. *Rubidge and Qua*, J. A. C. S., 1914, 732).

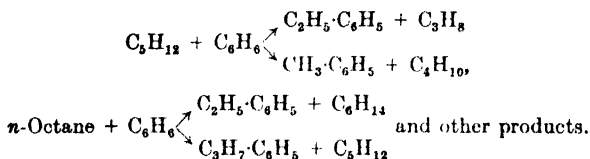
In certain cases the acyl chloride may form an additive compound with the hydrocarbon, e.g. hexene yields 2-chloro-cyclohexyl methyl ketone and this by loss of  $\text{HCl}$  gives tetrahydroacetophenone (*Wieland and Bettag*, B., 1922, 2246).

When antimony chloride is used an additive compound with the hydrocarbon is first formed, e.g.  $2\text{SbCl}_3$ ,  $\text{C}_6\text{H}_5\text{R}$ , which then reacts with the acyl chloride, e.g. benzoyl chloride, yielding an additive compound of the ketone and antimony chloride, which decomposes into its constituents at the temperature of the experiment; and the liberated  $\text{SbCl}_3$  can then react with fresh quantities of hydrocarbon (*Menschutkin*, Abs., 1914, i, 188, 673).

Aluminium chloride in the presence of a trace of hydrogen chloride can cause the fission of a paraffin hydrocarbon:



As a rule either  $\text{MeCl}$  or  $\text{EtCl}$  is split off from the complex hydrocarbon, so that with either *n*- or *iso*-pentanes and benzene the following reactions occur:

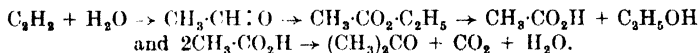


2 : 2 : 3-Trimethyl pentane,  $\text{CH}_3\cdot\text{CMe}_2\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CH}_3$ , and benzene give  $\text{CH}_3\cdot\text{CMe}_2\cdot\text{C}_6\text{H}_5 + \text{C}_4\text{H}_{10}$  (*J. Org.*, 1938, 137).

**Phosphoric acid** is used as a catalyst in the dehydration of alcohol to ethylene. Acetic acid (45 per cent yield) can be synthesized from methanol vapour and carbon monoxide in the presence of phosphoric acid and calcium phosphate (*Hardy*, J. C. S., 1934, 1335).

**Complex Reactions.**—By using a mixed catalyst it is possible to bring about several distinct reactions in one process.

One of these is the direct formation of acetone from acetylene:



The best catalyst is a mixture of reduced ferric oxide or metallic iron mixed with a little potassium carbonate or lime at a temperature of 450°. The yield is about 80 per cent, and the method is used commercially for producing acetone. If alcohol is used as starting material, the gaseous mixture contains 80 per cent of hydrogen and 20 per cent of CO<sub>2</sub>.

## L. STEREOCHEMISTRY \*

### A. Carbon

In preceding chapters (cf. pp. 179, 245, 286) attention has been drawn to the fact that compounds containing a carbon atom attached to four different radicals exist in two optically active isomeric forms and that the isomerism can be attributed to the spatial arrangements of the atoms within the molecule. All natural optically active compounds and all common ones prepared in the laboratory, e.g. valeric, lactic, and malic acids, active amyl alcohol, &c., contain two or more carbon atoms. *Pope* and *Read* (J. C. S., 1914, 811) succeeded in resolving a compound with only one carbon atom (chloriodomethanesulphonic acid,  $\text{CHCl}\cdot\text{SO}_3\text{H}$ ) by fractional precipitation with brucine, and in a similar manner the chlorobromo acid (J. C. S., 1925, 1572).

**Resolution of Racemic Compounds.**—Of the three methods introduced by *Pasteur* (Chap. X, D.) the formation of salts and the fractional crystallization has proved to be the most valuable for the resolution of synthetic racemic compounds, and *Pope* has introduced improvements on the original method. These comprise:

1. The use of a non-ionizing solvent in order to diminish the risks of racemization.

\* "Stereochemie", *K. Freudenberg*, Leipzig, 1933. "Stereochemie", *G. Goldschmidt*, 1933. "Some Aspects of Stereochemistry", *Mills, C. and L.*, 1932, 750.

2. The use of strong monobasic acids like camphor-sulphonic or bromocamphorsulphonic acid (cf. Camphor, Chap. LVII, C2). The salts of such acids are less liable to hydrolysis and usually crystallize remarkably well. They are monobasic and hence give rise to only one type of stable salt, whereas acids such as tartaric used by *Pasteur* can give both normal and acid salts.

3. The use of only half of the theoretical amount of acid required to combine with the base to be resolved, together with sufficient mineral acid (usually hydrochloric) to combine with the other moiety of the base. With a *d*-sulphonic acid the possible compounds are:

- (a) *d*-base + *d*-sulphonic acid.
- (b) *l*-base + *d*-sulphonic acid.
- (c) *d*-base + hydrochloric acid.
- (d) *l*-base + hydrochloric acid.

On cooling or evaporating the least soluble of these salts, either *a* or *b*, separates, and this destroys the equilibrium and ultimately all the sulphonic acid separates as, say, salt (*a*), leaving in the mother liquor the *l*-base as its soluble hydrochloride. The separation is easy and practically complete, and does not entail the numerous recrystallizations required by the older method.

In addition to the bases used by *Pasteur*, viz. the natural alkaloids, the following have been utilized: menthylamine, bornylamine and hydroxy-hydrindamine.

The fact that a particular racemic acid can be resolved by a particular *d*-base does not mean that the racemic form of the same base can be readily resolved by the *d* or *l* forms of the particular acid, e.g. if the *dBdA* and *dBIA* are readily separated it does not follow that *dBdA* and *lBdA* can also be readily separated.

Modifications of this method are the esterification of a racemic acid with an optically active alcohol (Chap. X, D.) or of a racemic alcohol by an active acid; or the resolution of *r*-aldehydes by use of an active phenylhydrazine, e.g. *d*-amylphenylhydrazine and hydrolysis of the resulting active hydrazone. For separation of *dl* bases (primary and secondary amines) an optically active aldehyde can be used.

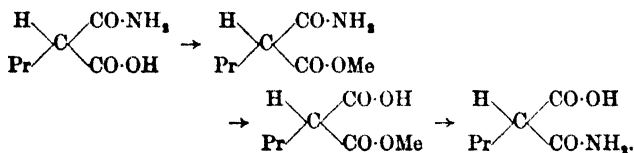
A different method was used by *Pickard* and *Kenyon* (J. C. S., 1912, 620), who combined the *r*-alcohol, ROH, with the anhydride of a dibasic acid to form an acid ester, e.g. the

hydrogen phthalate,  $\text{RO}\cdot\text{CO}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{OH}$ , which as a mono-basic acid forms two salts with an optically active base (an alkaloid). These can be fractionally crystallized and from each an optically active acid ester obtained, and on hydrolysis the two active alcohols.

The biochemical method has the great disadvantage that only one of the active compounds can be isolated, the other is destroyed by the organism, and as its action on the *d* and *l* forms is only relative it always follows that in order to obtain a relatively pure *d*-compound not only all the *l*-compound but some of the *d*-isomer is destroyed, and hence the loss is much greater than the theoretical 50 per cent. Dilute solutions have to be used, and hence large volumes of liquid are necessary to obtain appreciable amounts of active product, and as other enzymes are usually present a mixture of products difficult to separate is often formed.

An interesting case of spontaneous separation of the two stereo-isomers is described by *Neuberg* (*Biochemia*, 1937, 383) in the case of the potassium hexoates obtained by bacterial putrefaction. When kept for thirty years separation into crystals of *d* and *l* forms occurs.

An extremely interesting conversion of a *d*-compound into its *l*-isomeride without disturbing the attachment of the four atoms directly united to the asymmetric carbon atom has been accomplished by *E. Fischer* and *Brauns* (*Abs.*, 1914, i, 942) in the case of isopropylmalonamic acid. The changes are represented by the following scheme, where *Pr* represents the isopropyl group:



The change,  $\cdot\text{CO}\cdot\text{NH}_2 \rightarrow \text{CO}\cdot\text{OH}$ , was effected by means of nitrous acid, and  $\cdot\text{CO}\cdot\text{OMe} \rightarrow \cdot\text{CO}\cdot\text{NH}_2$  by means of the hydrazidic acid,  $\text{CO}_2\text{H}\cdot\text{CHPr}\cdot\text{CO}\cdot\text{NH}\cdot\text{NH}_2$ , which gave the azoimide,  $\text{CO}_2\text{H}\cdot\text{CHPr}\cdot\text{CON}_3$ , with nitrous acid, and this with ammonia the amide. The positions of the original  $\cdot\text{CO}\cdot\text{NH}_2$  and  $\cdot\text{CO}\cdot\text{OH}$  groups were thus interchanged, and resulted in an optical inversion.



It has been pointed out already (p. 182) that in a series of derivatives of an active compound, C a, b, c, x, the optical activity persists \* so long as x does not become identical with either a, b, or c. *Fischer* and *Flatau* (Abs., 1909, i, 628) have examined the case of propylisopropylacetic acid in which two of the groups have the same weight, and are similar but not identical. They find that the synthetic acid is readily resolved by means of brucine, and the *d*-acid has  $[\alpha]_D = +11.4^\circ$ . Propylisopropylcyanoacetic acid also exists in two active forms.

**Symmetry and Optical Activity.**—In the simple cases already discussed, viz. valeric, lactic, and tartaric acids, the enantiomorphous or nonsuperposable forms, which are the optically active forms, have been characterized by the absence of a plane of symmetry, and the internally compensated forms, e.g. mesotartaric acid and mucic acid, by the presence of a *plane of symmetry*. By the term plane of symmetry is understood a plane cutting the figure into two halves, such that the reflection of the one half in a mirror occupying the position of the dividing plane restores the missing half. This is clearly seen in the case of the mesotartaric acid model or projection III (p. 286).

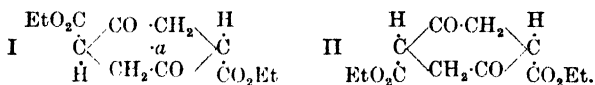
It has been assumed by many chemists that in all cases similar relationships hold good, namely, that the enantiomorphous or optically active forms are always devoid of a plane of symmetry and the superposable forms characterized by the presence of such a plane. This is not correct, as there are many arrangements of atoms which are not enantiomorphous although devoid of a plane of symmetry.

According to *Barker* and *Marsh* (J. C. S., 1913, 838), the essentials for enantiomorphism, and hence for optical activity, are the absence of (a) a plane of symmetry, (b) a centre of symmetry, and (c) an alternating axis of symmetry.

By *centre of symmetry* is meant a point in the middle of the molecule, such that a line drawn from any atom within the molecule to this point will meet a similar atom when produced in the opposite direction. By rotating the lower halves of the models I, II, and III on p. 286, it will be found that I and II have no such centre of symmetry and that III has. The

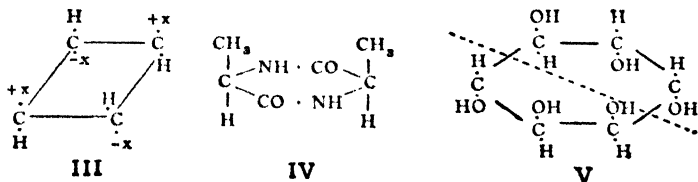
\* In some cases racemization may occur in transforming the compound into a derivative, but in such cases the product formed can be resolved into optically active components.

relationship is seen clearly in the case of certain cyclic compounds, e.g. ethyl succinylosuccinate (p. 539), ethyl trans-2:5-diketocyclohexane-1:4-dicarboxylate (I):



It is clear that a line drawn from any atom (or group) through the point *a* meets a similar atom (or group) on the opposite side of the molecule. The molecule contains a centre of symmetry or is centrosymmetric, and hence does not exist in enantiomorphous forms, and the possibility of optical activity is precluded. The cis compound II, on the other hand, has no such centre of symmetry, and should exist in optically active forms. For the analogous case of 1:4-diketo-2:5-dimethylpiperazines cf. *Fischer, B.*, 1906, 467, 3981.

*Alternating axis of symmetry.*—This is best illustrated by reference to a tetramethylene compound containing 4 asymmetric carbon atoms attached to the 4 carbon atoms of the ring, viz.  $\text{C}_4\text{H}_4(\text{C}a, b, c)_4$ , where *a*, *b*, and *c* are three different univalent radicals. In two cases these groups, *a*, *b*, *c*, are arranged in the +, and in two cases in the - order. It can be clearly seen by the aid of models that if any one group is rotated through an angle of  $90^\circ$  about the axis vertical to the plane of the 4-carbon ring, and the plane of this ring is regarded as a mirror, the group in question, whether H or C *a*, *b*, *c*, finds its reflection in the corresponding group below. The molecule as such is superposable upon its mirror image; the two are not enantiomorphous, and hence it should be impossible to resolve such a compound into optical isomerides.



The axis perpendicular to the plane of the ring is termed an alternating axis of symmetry (or sometimes a quaternary mirror axis). This case is quite different from that of the cis-succinylosuccinic ester (II, above), or the cis-1:4-diketo-

2 : 5-dimethylpiperazin. In the latter case (IV) the two methyl groups are represented in a plane above that containing the piperazine ring, and the two hydrogen atoms in a corresponding plane below. Although the molecule possesses none of the three elements of symmetry already enumerated, it contains an ordinary axis of symmetry, i.e. by simply rotating the molecule through  $180^\circ$  about this axis, which is perpendicular to the ring, each atom comes into congruence with a similar atom, and the molecule as a whole presents the same aspect before and after rotation; thus the molecule is not absolutely asymmetric, and yet it is enantiomorphous and its mirror image is not superposable. Two optically active forms should therefore exist, and *E. Fischer* has actually isolated such isomerides. The analogously constituted 2 : 5-dimethylpiperazine ( $\text{CH}_2$  in place of CO) has resisted all attempts to resolve it (*J. C. S.*, 1912, 2325). An analogous case is that of the optically active isonitols, hexahydroxycyclohexanes (p. 487) (V), where the ordinary axis of symmetry lies in the plane containing the 6 carbon atoms.

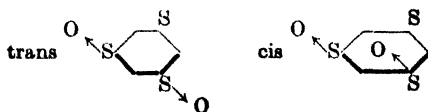
Several other types of enantiomorphous carbon compounds are worthy of notice:

### 1. CYCLOPARAFFINS

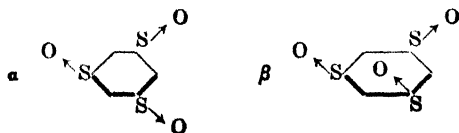
As explained in Chap. XVI a disubstituted derivative of a cycloparaffin can exist in two stereo-isomeric forms, viz. the *cis* and the *trans*, e.g.  $\text{C}_6\text{H}_{10}(\text{CO}_2\text{H})_2$ , *cis*- and *trans*-hexahydrophthalic acids. As pointed out the *cis*-compound is non-resolvable, whereas the *trans*- is a racemic form and can be resolved. Various methods have been used for determining which of the two compounds is the *cis* and which the *trans*. The following are some of the more important: (1) When the two substituents are alike, e.g.  $\text{C}_6\text{H}_{10}\text{X}_2$ , the *cis* form has a plane of symmetry, whereas the *trans*-compound is dissymmetric and capable of resolution, and when resolution can be brought about, e.g. an acid by means of an active alkaloid, the acid must have the *trans* configuration. (2) Ring formation by the substituents often gives a clue as to the configuration. In the case of dibasic acids with the  $\text{CO}_2\text{H}$  groups attached to adjacent carbon atoms of the ring, or even in 1 : 3-positions, one acid usually yields an anhydride quite readily, e.g. by gentle heating, whereas the other is relatively stable, and if it should form an

anhydride this yields the isomeric acid on hydration. Models show that in the *cis* acid the  $\text{CO}_2\text{H}$  groups are so placed that water can be readily eliminated and an anhydride formed. In a few cases the *trans* acid can also form a definite anhydride, e.g. by the action of acetyl chloride, but such anhydrides are unstable and when heated tend to pass over into the isomeric *cis* anhydrides. A similar method can be adopted in the case of lactone formation from 1:3- or 1:4-hydroxy-carboxylic acids. The reaction with boric acid can be used for 1:2-cycliglycols. Boric acid can react with 1:2-glycols forming spiro co-ordinated condensation products (Chap. XLVI, B.) of strongly acid properties. Only 1:2-glycols, where the two OH groups lie on the same side of the molecules (cf. Chap. XVI, p. 382), can yield such compounds, and the fact that the addition of the glycol to a boric acid solution increases the electric conductivity of the solution may be taken as a sure indication that the two OH groups are in *cis*-positions. (3) Steric hindrance. A comparison of the reaction velocities of the two compounds is often of value. Thus with the two 2-isopropyl-cyclohexane-1-ols one is esterified much more readily than the other, and is therefore regarded as the *trans*-compound as in the *cis*-compound the isopropyl group would have a retarding effect on the reaction of the adjacent hydroxyl group with the acid. (4) From a study of the number of isomers obtained by the introduction of a third substituent. Trithio-

formaldehyde,  $\text{CH}_2 \begin{array}{c} \nearrow \text{S} \cdot \text{CH}_2 \\ \searrow \text{S} \cdot \text{CH}_2 \end{array} \text{S}$ , yields two stereo-isomeric disulphoxides on further oxidation:



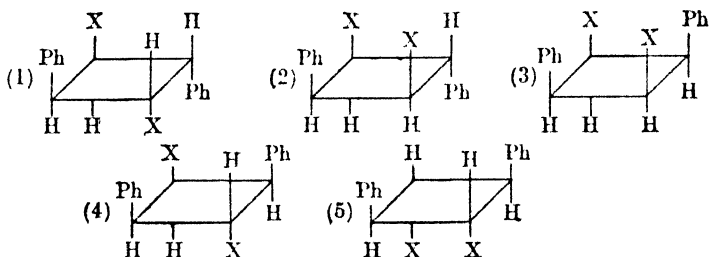
One of these yields only 1 trisulphoxide, whereas the other yields a mixture of two trisulphoxides:



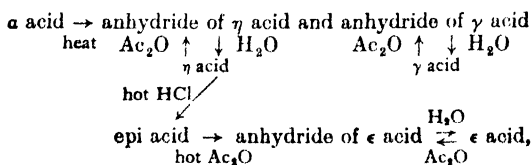
It is clear that it is the *cis* disulphoxide which yields the mixture of  $\alpha$  and  $\beta$  and the *trans* disulphoxide which yields the  $\alpha$ -compound only.

The stereochemistry of **cyclobutane** derivatives has received attention (p. 382), and in the case of the **truxillic acids**, 1 : 3-diphenylcyclobutane-2 : 4-dicarboxylic acids, the acids formed from cinnamic acid by additive ring synthesis, all the five possible stereo-isomerides, figs. 1 to 5, in which  $X = \text{CO}\cdot\text{OH}$ , have been isolated.

The configurations have been determined by means of (a) the formation of anilic acids resolvable into optically active forms (1 and 2), and (b) the facility of anhydride formation, i.e. the *cis*-positions of the carboxyl groups (2, 3 and 5).



The following scheme represents their relationships:

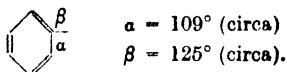


and the  $\alpha$  and  $\gamma$  acids give resolvable anilic acid, and hence the structure allocated to the five known acids are  $\alpha = 1$ ,  $\gamma = 2$ ,  $\eta = 3$ , epi = 4, and  $\epsilon = 5$ .

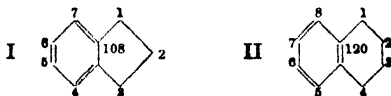
Stoermer, B., 1923, 676, 1683; 1924, 15; 1925, 2707. Of the six possible **truxinic acids**, 1 : 2-diphenylcyclobutane-3 : 4-dicarboxylic acids, also polymers of cinnamic acid, four have been actually isolated.

## 2. BENZENE AND NAPHTHALENE COMPOUNDS

*Mills and Nixon* (J. C. S., 1930, 2510) claim to have obtained evidence in favour of the *Kekulé* structure, and this is based on the argument that the angle  $\alpha$  which an external valency makes with a nuclear single link is smaller than the angle  $\beta$  which the external valency makes with a nuclear double link.



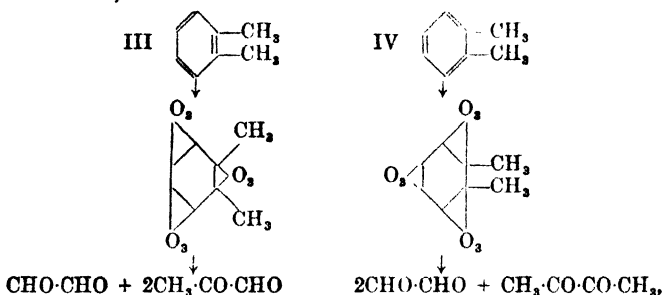
Comparing the compounds hydrindene and tetrahydronaphthalene, as the angle of a regular pentagon is  $108^\circ$  and that of a regular hexagon  $120^\circ$ , it is highly probable that hydrindene will have the structure I with no double link in the right-hand ring and tetrahydronaphthalene structure II with a double bond common to the two rings:



These conclusions are supported by the following evidence: As a rule when bromine or a diazonium salt reacts with an enol the substituent becomes attached to the carbon atom united to the C(OH) group by the double link, e.g.  $R \cdot CH_2 \cdot C(OH) : CH_2$  gives  $R \cdot CH_2 \cdot C(OH) : CHBr$  and not  $R \cdot CHBr \cdot C(OH) : CH_2$ , and similarly with the diazo-group. By analogy when a phenol undergoes ortho substitution with either bromine or a diazonium salt the Br or diazo-group will be attached to the C atom carrying the double link. When this test is applied to 5-hydroxy-hydrindene it is found that the product formed is the 6-bromo- or 6-diazo-compound indicating the presence of the olefine link between C atoms 5 and 6; *Sidgwick and Springatt* (*ibid.* 1936, 1532) arrive at the same conclusion from a study of the dipole moment of 5 : 6-dibromohydrindene. This is smaller (1.78) than that for ordinary ortho-dibromoderivatives, e.g. *o*-dibromobenzene, 5 : 6-dibromo-*o*-xylene, 6 : 7-dibromotetralin (all about 2.12), indicating the group  $\cdot CBr : CBr \cdot$  and not  $\cdot CBr \cdot CBr \cdot$ . *Fieser and Lothrop* (J. A. C. S., 1936, 2050) by proving that 5-methyl-6-hydroxy-hydrindene

does not couple with diazonium salts, whereas the 3-methyl-5-hydroxy-compound couples in the normal manner support structure I. 6-Hydroxy-tetrahydro-naphthalene gives the 5- and not the 7-bromo- or diazo-derivative.

An attempt by *Levine and Cole (ibid. 1932, 338)* to distinguish between the two formulæ III and IV for *o*-xylene by ozonization,



gave no definite result as the product was a mixture of all three ozonolysis compounds, and *o*-xylene is probably a tautomeric mixture or a resonance form of the two possible structures.

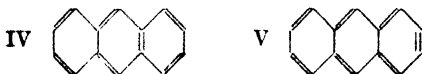
**Structure of Naphthalene.**—A large amount of evidence has been adduced in favour of the symmetrical structure I rather than the dissymmetrical formula II.



Thus there is close similarity in the properties of *o*-divinylbenzene and naphthalene. As the most stable form of *o*-divinyl benzene would be the one with all the double links conjugated (III), it follows that in naphthalene the two atoms common to the two rings are united by a double link (B., 1936, 715). Further support for this view is found in the behaviour of the 1:8-dialkyl-2:7-dihydroxy-naphthalenes. These compounds do not react with diazonium salts, as in the symmetrical formula the reactive hydrogen HC:C·OH has become replaced by alkyl, whereas in the unsymmetrical formula one such active group would be present (*Fieser and Lothrop, J. A. C. S., 1935, 1459*). The reactivity of  $\beta$ -naphthol and  $\beta$ -naphthylamine in position 1 and not in 3 also indicates a double link

between C atoms 1 and 2, a single link between 2 and 3; and further arguments are the non-formation of a quinone from 2:3-dihydroxy-naphthalene. On the other hand, dipole moments appear to indicate no definite fixation of bonds (J. C. S., 1936, 393).

An examination of 1:5-dialkyl-2:6-dihydroxy-anthracenes (J. A. C. S., 1936, 749) shows that these compounds do not react with diazonium salts, and hence the double links are between 1 and 2, 5 and 6 (IV) and not between 2 and 3, 5 and 6 (V).

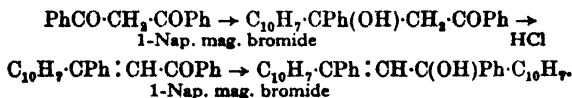


### 3. THE ALLENE GROUP

An **allene** derivative of the type  $\begin{matrix} a & & a \\ & \diagdown & / \\ & C:C & \\ & / & \diagdown \\ b & & b \end{matrix}$  has a dissym-

metric molecule as the groups *a* and *b* attached to the one carbon atom lie in a plane perpendicular to the plane of the two groups *a* and *b* attached to the other terminal carbon atom (fig. I, p. 782), and the compound should exist in two enantiomorphous, optically active forms. The possibility of such isomerides was pointed out by *van 't Hoff*, but several attempts to isolate them met with no success (cf. *Lapworth* and *Wechsler*, J. C. S., 1910, 38), but *Mailand* and *Mills* (J. C. S., 1936, 987) obtained an optically active 1:3-diphenyl-1:3-di- $\alpha$ -naphthyl-allene,  $C_{10}H_7 \cdot CPh:C:CPh \cdot C_{10}H_7$ , with a m.-pt.  $159^\circ$  and a rotation  $[\alpha]_{5461} + 437^\circ$  by the asymmetric dehydration of the alcohol,  $C_{10}H_7 \cdot CPh:CH \cdot C(OH)Ph \cdot C_{10}H_7$ , by means of an optically active catalyst, viz. *d*-camphor-sulphonic (1 per cent) in benzene solution.

The several stages from dibenzoylmethane were:



The active hydrocarbon is accompanied by appreciable amounts of the *r*-compound melting at  $224^\circ$ , which is much less soluble than the active form. By using the *l*-camphor-

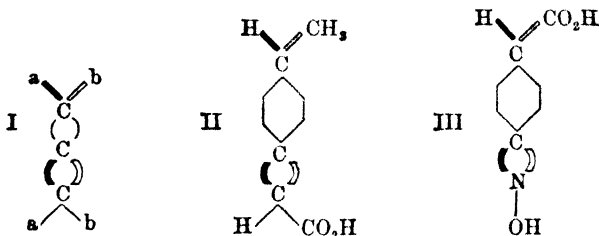


sulphonic acid the *l*-hydrocarbon is formed. The formation of the hydrocarbon is probably through the ester formed from the active acid and the *r*-alcohol, viz.  $C_{10}H_7 \cdot CPh \cdot (O \cdot SO_2 \cdot C_{10}H_{15}O) \cdot CH : CPh \cdot C_{10}H_7$ , followed by the dissociation of this into the bromocamphorsulphonate and the carbonium ion  $(C_{10}H_7 \cdot CPh \cdot CH : CPh \cdot C_{10}H_7)^+$ , which immediately decomposes into  $H^+$  and the allene.

If *d*-bromocamphorsulphonic acid is used the main product is the *r*-hydrocarbon.

Another active allene derivative is the acid,  $C_{10}H_7 \cdot CPh : C : CPh \cdot CO \cdot O \cdot CH_2 \cdot CO_2H$ , **carboxy-methyl-1:3-diphenyl-3-naphthyl-allene-1-carboxylate**, obtained by resolving the racemic acid with brucine.

Compounds somewhat similar to the allene type are the cyclohexylidene derivatives, e.g. 1-methylcyclohexylidene-4-acetic acid, II, in which one of the olefine links in allene is expanded into a 6 carbon ring. This ring like the double link prevents free rotation.



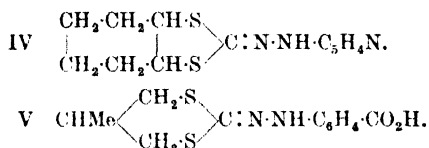
In these projections the thin lines represent bonds lying in the plane of the paper, thick lines bonds in a plane above that of the paper, and the double lines,  $\square$  and  $\square$ , bonds in a plane below that of the paper.

The synthetic 1-methylcyclohexylidene-4-acetic acid has been resolved by means of brucine (*Pope, Perkin, and Wallach, J. C. S., 1909, 1789, cf. ibid. 1510*).

The two forms have m.pt.  $53^\circ$  and  $[\alpha]_D \pm 81^\circ$ . The dibromides of the active acids are also optically active as the C atom in the  $\alpha$ -position to the carboxylic group has become a centre of dissymmetry. The activity also persists when HBr is removed by alkali and an  $\alpha$ -bromo-acid,  $>C : CBr \cdot CO_2H$ , or even when HBr and  $CO_2$  are eliminated and an active bromo-compound  $>C : CHBr$  formed.

An analogous compound is 4-oximino-cyclohexane-1-carboxylic acid, III, which has been resolved by *Mills and Bain* (*ibid.* 1910, 1866) by means of morphine and quinine. The active sodium salts were obtained, but when acidified with hydrochloric acid an inactive acid was formed.

The corresponding phenylhydrazones and semicarbazones have also been resolved (1914, 64), and other compounds of somewhat similar type which have been resolved are the pyridylhydrazone of cyclohexylene-dithiocarbonate (1923), IV, and *o*-carboxyphenylhydrazone of methyltrimethylene-dithiocarbonate (1931), V.

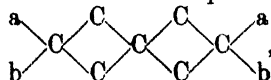


The accumulation of so many cases of optically active compounds containing the grouping  $>\text{C:N}\cdot\text{R}$  is a strong argument in favour of *Hantzsch* and *Werner's* view (this Chap., C1) that when a tervalent nitrogen atom is attached to carbon by a double link the three valencies of the nitrogen atom do not lie in a single plane.

All are readily racemized and the group of compounds are less symmetric than the true allene compounds which have an axis of symmetry.

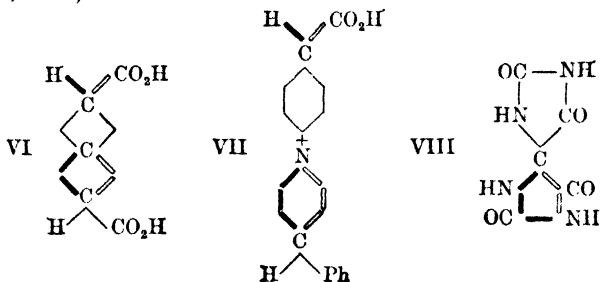
#### 4. THE SPIRAN GROUP

If both olefine links in an allene are expanded into rings a true spiran results,



substituted spirans the stereochemical relationships are similar to those of the allene and *cyclohexylidene* compounds. Thus cyclobutanespirocyclobutane-1:1'-dicarboxylic acid, VI, and the corresponding diamine are resolvable (*Baeker and Schurink*, *Rev.*, 1931, 921, and *Janson and Pope*, *C. and I.*, 1932, 316). Analogous compounds with two six-membered rings (4 C and 2 O) and with Me and CO<sub>2</sub>H or H and ·CH<sub>2</sub>·NH<sub>2</sub> attached to

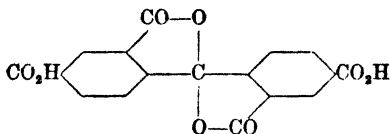
the *p* and *p'* carbon atoms are also resolvable (B., 1928, 1855; 1929, 1310).



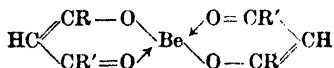
For an example with an N ion common to the two rings (VII) cf. *Mills and Warren*, J. C. S., 1925, 2507.

Another example is spiro 5:5'-**dihydro hydantoin**, VIII, where the asymmetry is due to the two sides of the ring being different, e.g. NH·CO and CO·NH. It has been resolved by brucine (*Pope and Whitworth*, P. R. S., 1931, A., 134, 357).

Analogous to VIII is the ketodilactone of benzophenone-2:4:2':4'-tetracarboxylic acid which has been resolved by means of *l*-α-phenyl-ethylamine (*Mills and Nodder*, J. C. S., 1921, 2094),



Numerous resolvable spiro compounds are met with in co-ordinate chelate compounds with a quadrivalent Be, Cu, or Ni atom common to the two rings, e.g.:



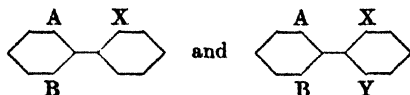
## 5. DIPHENYL DERIVATIVES \*

As stated in Chap. XXVII the great majority of diphenyl derivatives can be represented by a uniplanar structure in

\* For summary cf. *Adams and Yuan*, Chem. Rev., 1933, 261.

which the axes of the two rings lie in a straight line, i.e. by coaxial and coplanar nuclei. The existence of certain isomerides and the formation of certain complex cyclic derivatives which were used as arguments in favour of a biplanar, e.g. *Kauffler*, formula have been shown to be illusory (*Turner*, J. C. S., 1920, 1140; 1926, 2476; 1927, 2330).

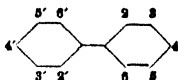
The values of the dipole moments of 4:4'-disubstituted derivatives of diphenyl point to the uniplanar structure as many of these compounds—like the corresponding *p*-disubstituted benzenes—are non-polar. The resolution of 6:6'-dinitrodiphenic acid by *Kenner* and others in 1921 into *d*- and *l*-optically active forms and the subsequent resolution of other acids containing substituents in the 6 or 6:6'-positions brought the configuration of these compounds again into prominence, and the view put forward to account for the phenomena and now generally accepted (*Turner* and *Le Fevre*, J. S. C. I., 1926, 831; *Ball* and *Kenyon*, 864; *Mills*, 883, 903) is that in these 6- or 6:6'-substituted derivatives of diphenic acid the ortho-substituents tend to push the planes of the rings apart, either by purely mechanical or a combination of mechanical and polar forces, i.e. the two nuclei are no longer coplanar and unrestricted free rotation about the common axis is no longer possible, e.g. in the case of a 6-nitro-diphenic acid the carboxylic group attached to the second nucleus can pass neither the nitro nor the carboxylic group of the first nucleus and hence a dissymmetric structure is formed and *d*- and *l*-isomerides become possible. This steric hindrance is not met with when substituents are in positions 3, 4 or 5. It has been found that the alkaloidal salts of acids such as 4:4'-diphenic acid exist in isomeric forms with activities due to the alkaloid and to an active anion; on liberating the free acid, however, it is found to be inactive. This indicates that in the salt the two benzene nuclei are not coplanar, but become so as soon as the free acid is formed (J. C. S., 1922, 616; A., 1927, 455, 272). If this view is correct then in the types



resolution into active forms should be possible in all cases where A and B are different, and X and Y are different from

each other although neither need necessarily be different from A or B. This type of isomerism, which is very similar to that in the allenes is due to steric hindrance and is to be found in other types of compounds (section 6).

Some 30 acids (containing  $\text{CO}_2\text{H}$  or  $\text{SO}_3\text{H}$  substituents) and bases (with  $\text{NH}_2$  substituents) have been resolved by means of optically active bases, e.g. brucine or optically active acids. Many of these are derivatives of diphenic acid, diphenyl-2:2'-dicarboxylic acid,



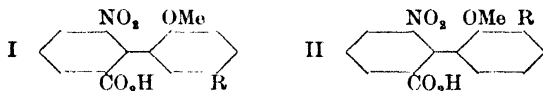
viz. 6-nitro-, 4:6'-dinitro-, 4:6-dinitro-, 6:6'-dichloro-, 6:6'-dinitro-, 4:4':6-trinitro-, 6:6'-dimethoxy; also derivatives of the 4:4'-dicarboxylic acid, viz. 2:2'-di-iodo-, 2:2'-dinitro-6:6'-dichloro; the pentanitro-3-carboxylic acid; derivatives of 3:3'-dicarboxylic acid, e.g. the 2:2'-difluoro-5:5'-dimethyl-, and numerous derivatives of the 2-nitro-6-carboxylic acid with Cl, Br, Me,  $\text{NO}_2$ , OMe in 2', and also similar compounds with Me, OMe, Cl, Br in 5'. The diphenyl-2:2'-disulphonic acid and the bases 2:2'-dimethoxyl-6:6'-diaminodiphenyl and substituted derivatives, 2:2'-difluoro-6:6'-diamino-3:5:3':5'-tetramethyl-diphenyl and diamino-dimesityl  $\text{H}_2\text{N}\cdot\text{C}_6\text{HMe}_3\cdot\text{C}_6\text{HMe}_3\cdot\text{NH}_2$ . Practically all these acids when obtained in an active form are stable and do not readily racemize; an exception is 4:6:4':6'-tetrabromodiphenic acid, although it has all four ortho-positions in the diphenyl molecule substituted (J. C. S., 1935, 206).

The following derivatives of diphenyl have resisted all attempts to resolve them: the 2:2'-dicarboxylic acid, 4'-nitro- and 4:4'-dinitro-diphenic acids, the monomethyl ester of diphenic acid, 4-nitro-3:2'-dicarboxylic acid 4:4'-dinitro-2:3'-dicarboxylic, 4-nitro-2':3-dicarboxylic acid, and 5:5'-dichloro-3:3'-dicarboxylic acid and several other compounds (1928, 1913; A., 1927, 455, 272; J. A. C. S., 1928, 2499; B., 1929, 2817).

Between the non-resolvable compounds and the stable active isomerides is a group of compounds which can be resolved but which are relatively unstable and racemize more or less readily when isolated as free acids or free bases. On the whole trisubstituted diphenyl racemize more readily than

tetrasubstituted compounds, although the character and size of the ortho-groups play an important part, e.g. 3 : 5 : 3' : 5'-tetramethyl-2 : 2'-difluoro-, 6 : 6'-diamino-diphenyl acids racemize readily, but the base 2 : 4 : 6 : 2' : 4' : 6'-hexamethyl-3 : 3'-diamino-diphenyl less readily.

Adams and others (J. A. C. S., 1932, 4434; 1934, 1787) have examined the two series of compounds:



where R = H, OMe, Me, Cl, Br, NO<sub>2</sub>, and find that a substituent in the 3'-position has a greater stabilizing effect than the same group in the 5'-position, perhaps due to its repulsing action on the methoxy group. As determined by half life the 3'-nitro-group has some 50 times the influence of the 5'-nitro-group.

In some cases, where it is difficult to isolate the acid, racemization can be detected by the mutarotation of the alkaloid salt solution.

The base 2 : 6-dibromo-3 : 3'-diamino-4 : 4'-ditolyl can be partially resolved by camphor-sulphonic acid although only 2-ortho-substituents are present. In the 2-nitro-2-alkoxydiphenyl-6-carboxylic acid, CO<sub>2</sub>H·C<sub>6</sub>H<sub>3</sub>(NO<sub>2</sub>)·C<sub>6</sub>H<sub>4</sub>·OR, the order of racemization is OMe > OEt > OPr (J. C. S., 1935, 1565); the 2'-methoxy group has little obstructing power; a comparison of F, Cl and Br in the 2'-position in the 6-nitrodiphenyl-2-carboxylic acid shows that the active chloro- and bromo-acids are relatively stable and racemize only slowly, whereas the fluoro-acid, as its brucine salt, racemizes rapidly. The fluorine atom is less effective than the methoxy group in preventing rotation, and it has not been found possible to resolve 2 : 2' : 6 : 6'-tetrafluoro-3 : 3'-dichloro-diphenyl-5 : 5'-dicarboxylic acid, although all 4-ortho-positions are substituted by F. The introduction of a substituent in position 5' in the 2-nitro-2'-methoxydiphenyl-6-carboxylic acid affects the stability of the acid and of the substituents examined, viz. OMe, Me, Cl, Br, NO<sub>2</sub>, the increased stabilizing effect is in the order given.

A study of the relative rates of racemization of the 2 : 2'-dimethoxy-6 : 6'-amides of the type OMe·C<sub>6</sub>H<sub>3</sub>(CO·NR<sub>1</sub>R<sub>2</sub>)·

$C_6H_3(OMe)CO \cdot NR_1R_2$  has given the following results (*Hsing* and *Adams*, J. A. C. S., 1936, 587).

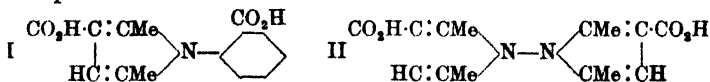
$R_1$	$R_2$	Half racemization in hours
H	H	4.5
Me	Me	3.75
Et	Et	19.5
H	Me	45
H	Et	156

according to which  $\cdot CO \cdot NH_2$  is more effective than  $\cdot CO \cdot NHMe$ , perhaps due to the former acting in the form  $\cdot C(OH) : NH$ .

Although diphenic acid with carboxyl groups in positions 2 : 2' cannot be resolved, compounds like 2-(hydroxy-diphenyl-methyl)-diphenyl-2'-carboxylic acid,  $CO_2H \cdot C_6H_4 \cdot C_6H_4 \cdot CPh_2 \cdot OH$ ; the 2 : 2'-disulphonic acid,  $SO_3H \cdot C_6H_4 \cdot C_6H_4 \cdot SO_3H^*$ ; benzidine-2 : 2'-disulphonic acid,  $SO_3H \cdot C_6H_3(NH_2) \cdot C_6H_3(NH_2) \cdot SO_3H$ ; *o*-(2-diphenylaminophenyl)-phenyltrimethyl ammonium iodide,  $NPh_2 \cdot C_6H_4 \cdot C_6H_4 \cdot NMe_3I^\dagger$ ; 2 : 2'-di-iodo-diphenyl-4 : 4'-dicarboxylic acid,  $CO_2H \cdot C_6H_3I \cdot C_6H_3I \cdot CO_2H$ , all of which contain only two ortho-substituents, have been resolved and even compounds with one *large* ortho-substituent can be resolved, e.g.  $AsMe_3I$  in 2 and Br in 3' (*C. and I.*, 1935, 19).

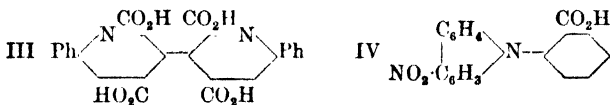
A phenyl- $\alpha$ -naphthyl with two ortho-substituents in the phenyl group can be resolved, e.g. 3 : 5-dinitro-2- $\alpha$ -naphthyl-benzoic acid,  $CO_2H \cdot C_6H_2(NO_2)_2 \cdot C_{10}H_7$  (*J. C. S.*, 1931, 1188), and also a derivative of  $\alpha\alpha'$ -dinaphthyl with one substituent in each naphthyl group, e.g. 1 : 1'-dinaphthyl-8 : 8'-dicarboxylic acid,  $CO_2H \cdot C_{10}H_6 \cdot C_{10}H_6 \cdot CO_2H$  (*J. A. C. S.*, 1931, 3104), or even with 1 carboxylic acid in one group, viz. the 1 : 1'-dinaphthyl-8-carboxylic acid,  $C_{10}H_7 \cdot C_{10}H_6 \cdot CO_2H$ , by means of brucine (*B.*, 1932, 32), but 2-*o*-tolyl-diphenyl-2'-carboxylic cannot be resolved (1934, 2650).

*Adams* and his co-workers (*J. A. C. S.*, 1931, 374; 1932, 1977; 1933, 1069, 4234) have shown that in compounds in which one or both phenyl radicals are replaced by heterocyclic nitrogen groups similar phenomena are observed; thus the compounds



\* As strychnine hydrogen salt.

† As camphor-10-sulphonate.



I. 1-*o*-Carboxyphenyl-2:5-dimethylpyrrole-3-carboxylic acid.

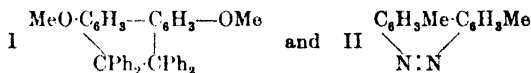
II. 2:5:2':5'-Tetramethyl-1:1'-dipyrrolyl-3:3'-dicarboxylic acid.

III. 2:4:2':4'-Tetracarboxy-6:6'-diphenyl-3:3'-dipyridyl.

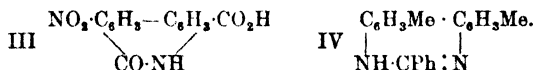
IV. 9-*o*-Carboxyphenyl-2-nitro-carbazole.

One of the obstacle (ortho) groups in an optically active diphenic acid can be replaced by another without destroying the optical activity, e.g. the  $\text{CO}_2\text{H}$  group in the active 2-nitro-6-methyldiphenyl-2'-carboxylic acid can be replaced by  $\text{NH}_2$ , by either the *Hofmann* or the *Curtius* reaction, and the resulting amine is active and the active 2:2'-diamino-6:6'-dimethyldiphenyl can be converted into an active 2:2'-di-iodo- or 2:2'-difluoro-compound (*Bell*, J. C. S., 1934, 835).

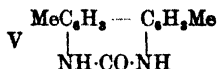
In many cases where cyclization occurs between the 2:2'-positions the products are non-resolvable, e.g. I and II (*B.*, 1935, 928):



and an active 6-nitro-6'-acetaminodiphenic acid yields an inactive ring compound III:



In a few cases optical activity is retained after cyclization; *Sako* (Abs., 1932, 524) has shown that the active *l*-3:3'-diamino-2:2'-ditolyl,  $\text{NH}_2\cdot\text{C}_6\text{H}_3\text{Me}\cdot\text{C}_6\text{H}_3\text{Me}\cdot\text{NH}_2$ , is converted through its monobenzoyl derivate by phosphorus trichloride at  $125^\circ$  into a *l*-2-phenyl-7:8-dimethyl-diphenimidine, IV, and the same diamine heated with urea at  $210^\circ$  yields *l*-2-keto-7:8-dimethyl-2:3-dihydrophenimidine, V.



This may be due to the two phenyl rings being coaxial but not coplanar.

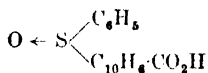


## 6. OTHER CASES OF RESTRICTED ROTATION

Other cases of restricted rotation producing dissymmetry and hence resolvable compounds are:

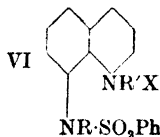
1. 8-Nitro-1-benzene-sulphonylglycinenaphthalene, i.e.  $\text{NO}_2$  and  $\cdot\text{N}(\text{SO}_2\text{Ph})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , in *peri*-positions in the naphthalene molecule, where the nitro-group interferes with the free rotation of the substituted  $\cdot\text{NH}_2$  group around the axis attaching N to the C of the naphthalene ring (*Mills and Elliott, J. C. S., 1928, 1291*).

2. Phenyl-8-carboxy-1-naphthylsulphoxide,

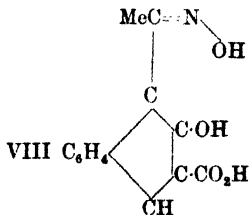
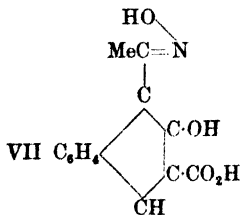


(*Rule and Turner, 1935, 319*).

3. 8-Substituted N-alkylquinolinium salts, e.g. VI, which can be resolved by  $\alpha$ -bromo- $\pi$ -sulphonic acid when  $\text{R}' = \text{Et}$  or larger group.

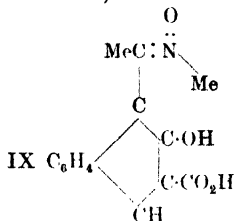


4. Of the two stereo-isomeric oximes VII and VIII,  $\alpha$ -2-hydroxy-3-carboxy-1-naphthyl methyl ketoxime,

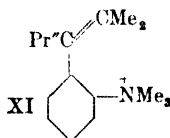
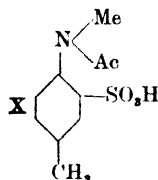


it is only the compound VIII with the OH of the oxime vicinal

to the phenolic OH which can be resolved. The N-methyl ether IX can also be resolved,



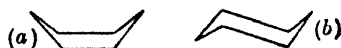
*Mills* and his co-workers have succeeded in resolving certain substituted benzene derivatives, viz. N-acetyl-N-methyl-*p*-toluidine-3-sulphonic acid, X, by means of brucine (J. C. S., 1937, 274), and *o*-( $\beta\beta$ -dimethyl- $\alpha$ -isopropyl-vinyl)-phenyl-trimethylammonium iodide, XI, by means of  $\alpha$ -bromocamphor-sulphonic acid (*ibid.* 1939, 460).



The optical activity is attributed to the dissymmetry of the molecule due to the restricted rotation about the single bond, C—N in X and C—C in XI, due to the presence of the relatively large ortho-substituent (SO<sub>3</sub>H in X and NMe<sub>3</sub> in XI). With the group ·CEt:CMe<sub>2</sub> in XI resolution is not possible.

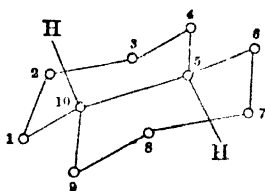
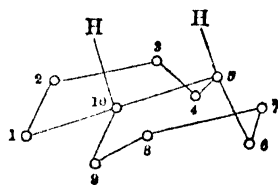
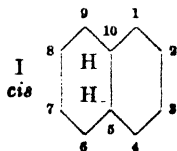
## 7. DICYCLIC SYSTEMS\*

It is now clearly established that saturated cyclic structures containing many more than 6 or 7 carbon atoms can exist and that many of them, when once formed, are comparatively stable (Chap. XXXIII). It can be shown that the strain in such rings can be relieved when a multiplanar configuration is adopted. In the case of cyclohexane the two possible configurations depicted by *Sachse* (B., 1890, 1363) are: (a) 4



\* *Mills*. Thorpe's Dic. Supp., Vol. II.

carbon atoms in one plane and the two remaining carbon atoms Nos. 1 and 4 in a second plane (*cis* form); (b) 4 carbon atoms in one plane and then Nos. 1 and 4 respectively above and below this plane (*trans* form). Such arrangements necessitate the existence of many isomeric simple substituted derivatives of cyclohexane, and as these do not appear to exist, the uniplanar formula for the six carbon atoms is generally accepted. The matter is quite different, however, when condensed polynuclear systems are examined, e.g. decahydronaphthalene (*Mohr, J. pr.*, 1918, [11], **98**, 315). Here the 6 carbon atoms, 2, 3, 5, 7, 8 and 10 are in one plane, and the atoms 1, 4, 6 and 9 in a second plane; then the two hydrogen atoms attached to Nos. 5 and 10 will both lie on the same side of the six-carbon plane, e.g. below, and the second carbon plane (4 atoms) will be on the other side of the six-carbon plane, e.g. above; *cis* configuration I. On the other hand, 2, 3, 5, 7, 8 and 10 may form one plane, 1 and 9 a second plane, and 4 and 6 a third plane. Then the H atom attached to No. 10 will be on one side the six-carbon plane and H atom attached to No. 5 will be on the other side. Two non-resolvable stereoisomeric decahydronaphthalenes, decalins, corresponding with the formulæ I and II are therefore possible,

*trans**cis*

Such pairs of stereoisomerides have actually been isolated: *cis* and *trans*-hexahydrohomophthalic acid anhydrides (CO in 2 and 4 and O in 3); two 2-ketodecahydronaphthalenes, decalones (CO in 2), and two decalins.

The two decalins (Hückel, A., 1925, 441; B., 1925, 1449) are best formed by the reduction of the *cis*- and *trans*- $\beta$ -decalones by amalgamated zinc and hydrochloric acid, but can also be obtained by careful fractionation of the decalin obtained from naphthalene (B., 1924, 683, 1639). They differ appreciably in physical properties, e.g. m.-pt.  $-51^{\circ}$ ,  $-36^{\circ}$ ; b.-pt.  $193^{\circ}$ ,  $185^{\circ}$ ;  $d_4^{20}$  0.896, 0.871;  $n_D^{20}$  1.481, 1.470. Heats of combustion 1500, 1495 cal./mol. (The first number given is for the *cis* and the second for the *trans*.)

On the whole the *cis*-compounds are less stable than the *trans*-, e.g.  $\text{AlCl}_3$  at room temperature isomerizes the *cis*-compound. The *cis* and *trans* configuration follows from this relationship to the decalones, and the configuration of these follows from the products of oxidation; both ketones yield two ortho-substituted acids derived from cyclohexane, viz.  $\text{CO}_2\text{H}\cdot\text{C}_6\text{H}_{10}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  and  $\text{C}_6\text{H}_{10}(\text{CH}_2\cdot\text{CO}_2\text{H})_2$ , but in the one case the *cis* forms are obtained and in the other the *trans*, indicating respectively the *cis*- and *trans*-positions of the two tertiary hydrogens in the two decalones.

The same type of isomerism is met with whenever two cycloparaffin rings are fused so that they have two rings in common, and is usually referred to as *cis*- and *trans*-decalin fusion (cf. Chap. LXII).

By the introduction of a substituent X into the decalin molecule, e.g. in position 2 four optically inactive forms, viz:

- (i) X in position 2, *cis* to both H No. 5 and H No. 10.
- (ii) X in position 2, *trans* to both H No. 5 and H No. 10.
- (iii) X in position 2, *cis* to H No. 5 and *trans* to H No. 10.
- (iv) X in position 2, *trans* to H No. 5 and *cis* to H No. 10.

Kay and Stewart (J. C. S., 1926, 3038) have isolated 3 of the 4 possible decahydronaphthoamides with  $(-\text{CO}\cdot\text{NH}_2)$  in position 2. They melt respectively at  $139^{\circ}$ ,  $165^{\circ}$  and  $195^{\circ}$ .

Hückel (A., 1927, 451, 109; 1933, 502, 99) has isolated all four possible 2-hydroxy- and 2-amino-decahydronaphthalenes by the reduction of the two  $\beta$ -decalones and their oximes respectively.

Numerous octalins (one olefine link) have also been prepared, including the  $\Delta^1$ ,  $\Delta^2$ ,  $\Delta^{1(9)}$  and  $\Delta^9$  (A., 1929, 424, 121; 477, 99; 1933, 502, 136), and their structures established by

ozonolysis. The  $\Delta^{1(9)}$ - and  $\Delta^9$ -octalins (respectively I and II) are



interesting as they form an exception to *Bredt's* rule that olefine links do not as a rule occur at bridge-heads. The  $\Delta^{1(9)}$  compound on ozonization yields  $\gamma$ -2-ketocyclohexylbutyric acid, III, and on further oxidation  $\delta$ -ketosebacic acid,  $\text{CO}_2\text{H} \cdot (\text{CH}_2)_4 \cdot \text{CO} \cdot (\text{CH}_2)_3 \cdot \text{CO}_2\text{H}$ . The  $\Delta^{1(9)}$  hydrocarbon is stable, is without strain, and gives a normal heat of combustion. The  $\Delta^9$ -compound on ozonolysis yields cyclodecane-1 : 6-dione, IV:



The method of ozonolysis is of value for determining the position of the double bond in the other octalins.

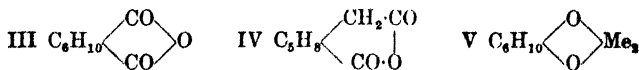
By the fusion of a 6 and a 5 carbon ring a compound **hydrindane** (hexahydrohydrindene), I, and such a compound shows the *cis-trans* types of fusion (B., 1923, 91; A., 1933, 505, 2714; B., 1934, 2104; J. C. S., 1934, 946), and similarly



with hexahydro- $\beta$ -hydrindone, II. In the latter case the compounds are formed respectively by the condensation of ethyl *cis*- and *trans*-cyclo-hexane-1 : 2-diacetates with sodium ethoxide (A., 1926, 451, 132). When reduced the *cis*-ketone yields a pair of meso (inactive) alcohols, whereas the *trans*-compound gives a racemic alcohol.

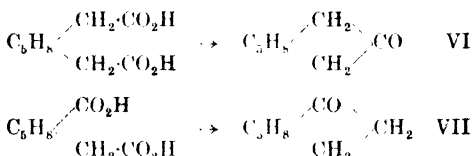
The *cis* form of the ketone is more stable than the *trans*, a result which cannot readily be reconciled with the tetrahedral conception of certain valencies.

Numerous other types of 6, 5 fused rings are known, e.g. anhydride of hexahydrophthalic acid, III, anhydride of cyclopentane-1-carboxylic-2-acetic acid, IV (J. C. S., 1934, 956), and, V, the



product formed by the condensation of acetone with *cyclohexylene glycol*. In all these cases the stability agrees with the requirements of the tetrahedral theory.

With five-five dicyclic systems the *cis* form is nearly strainless and more stable than the *trans* (cf. *Linstead and Cook*, J. C. S., 1934, 935), viz. VI and VII:

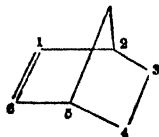


Quinoline can also give rise to a *cis* and *trans* decahydro-derivative (A., 1927, **453**, 163) and similarly tetrahydrocarbazoles (J. C. S., 1927, 2676). *Perkin and Sedgwick* (J. C. S., 1924, 2437; 1926, 438, cf. A., 1927, **455**, 171) have obtained 4 optically active tetrahydroacridines. For other cases see J. C. S., 1928, 639, 2583; 1929, 1861, 1975.

For enumeration of the number of isomeric forms of certain hydrogenated polynuclear systems see *Ingold*, Rep., 1924, 94.

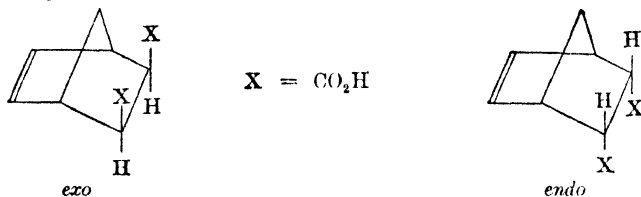
**Additive Compounds of Maleic Anhydride and Dienes.**—*Alder and Stein* (A., 1934, **514**, 1, 197, 211; 1935, **515**, 165, 185; 1936, **525**, 183) have dealt with the stereochemistry of the additive compounds of maleic anhydride with *cyclo-pentadiene* and related reactions (*Diels-Alder* reaction).

By the addition of the anhydride the diene is converted into a *cyclopentene* with a bridge of 2 C atoms (or it may be regarded as a *cyclohexene* with a CH<sub>2</sub> bridge). The dicyclic system is non-planar. In the hexene ring 4 C atoms (1, 2, 5, 6) lie in one plane, two (3, 4) in a different plane, and the bridge CH<sub>2</sub> (7) in a plane above the two planes. The carboxylic groups

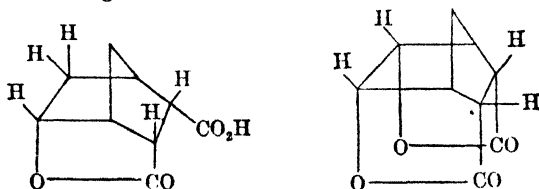


will be *cis* to one another, and either both directed towards

the  $\text{CH}_2$  bridge (*Ero form*) or both away from the bridge (*Endo form*).



They show that the addition product is the *Endo* compound by the following series of reactions. By the action of aqueous bromine on the additive compound a product with Br and OH attached to the olefine link results. With acetyl chloride this loses water, giving the monolactone, I, which with alcoholic alkali gives the dilactone, II.



In a similar manner it was shown that the addition of maleic anhydride to methyl *cyclopentadiene-1-carboxylate* takes place giving the *Endo* products only. (For summary cf. Rep., 1936, pp. 238-245.)

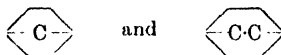
**Stability of Dicyclic Systems** (*Hückel*, 1927).<sup>\*</sup>—(1) Two five-membered rings can be fused by *cis*-valencies to yield a strain-free rigid structure containing two inclined planar rings, whereas fusion by *trans*-valencies gives a rigid strained multiplanar structure in which the minimum strain is almost equal to that of the camphor system. (2) Two six-membered rings can be joined by either *cis*- or *trans*-valencies to yield strainless multiplanar structures, the *cis* form being mobile and the *trans* comparatively rigid. (3) A five-membered ring can be fused to a six-membered ring by *cis*-valencies to give a strainless structure. *Trans* linking of these rings gives a strained multiplanar structure in which the minimum strain is about half that given by the *trans* linking of two five-membered rings.

<sup>\*</sup> Cf. *Linstead*, Rep., 1935, 306.

The relative strains in a pair of isomers can be determined:

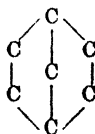
- (1) By the composition of the equilibrium mixture of the two under given conditions, as the greater the strain the greater the readiness to pass over into the less strained isomer.
- (2) A more exact method is from the relative heats of combustion and hence of heats of formation, but here it is found that as a rule a *cis*-compound has a heat of combustion of about 2 Kg. cal. as compared with its *trans* isomer quite independent of relative strains. For the decalins the difference in heats of combustion of the two is (*trans* - *cis* = -4.7 Kg. cal.), for  $\beta$ -hydrindanones -1.1, for hydrindanes -1.8, and for bicyclooctanes +6.1.

For strains in certain bridged systems cf. *Alder* and *Stein*, B., 1934, 613.



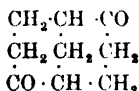
Bridged rings with 3 atoms common to both rings.

The commonest type is camphane of the 1:2:2 type



(Chap. LVII, C.), i.e. two *cyclopentane* rings with three C atoms common to both. Such systems exhibit considerable strain and hence have high energy content as shown by their abnormally high heats of combustion.

On the other hand, a compound of the 1:3:3 type, e.g. bicyclononadione is quite stable,



(A., 1913, 398, 169), and is readily formed from formaldehyde and ethyl malonate.

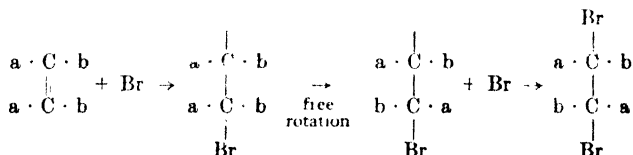
**Multinuclear Compounds.**—Most multinuclear compounds, e.g. naphthalene, anthracene, phenanthrene, &c., have planar configurations, whereas pure fluorene (Chap. XXVIII), obtained from fluorenoneoxime, when subjected to X-ray crystallographic



examination, shows a non-planar molecule (*Cook and Iball, C. and I., 1936, 467*), and in all probability the planes of the six-membered rings are inclined at an angle of  $20^\circ$  to that of the five-membered ring and at an angle of  $40^\circ$  to each other.

## 8. STEREOCHEMISTRY OF OLEFINE DERIVATIVES

Compounds of the types  $abC:Cab$  or  $abC:Cde$  exist in *cis* and *trans* forms which are inactive and relatively stable, but under the influence of traces of halogen and of sunlight the more labile is converted into the more stable form (*Chap. X, B.*). *Berthoud* (*J. Chem. phys.*, 1927, 213; 1928, 40; 1930, 290), by a study of the rate of the conversion of *allo*-cinnamic into cinnamic acid by exposure of benzene solutions containing a trace of bromine or iodine as catalyst to ultra-violet light, has shown: (1) Under constant illumination the *trans* formation is directly proportional to the concentration of the *allo*-acid. (2) The rate varies as the square root of the intensity of the light, indicating that each quantum of light absorbed must produce two active atoms, e.g.  $Br_2 \rightarrow 2Br$ .



(3) When the light is completely absorbed the rate is independent of the concentration of the catalyst since the concentration of halogen atoms is limited by the amount of light absorbed. When more light energy is available than can be absorbed, the rate of transformation is proportional to the square root of the catalyst concentration since the number of molecules activated is proportional to the total concentration of the catalyst and each activated molecule supplies two active atoms. The reaction is an example of a "chain reaction" (*cf. Chap. LI, B., and LX, C1*).

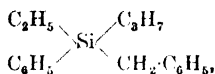
Other cases, e.g.  $\alpha$ -phenyl-cinnamionitrile,  $PhCH:CPh-CN$ , are more complex.

It is claimed that this concept accounts for the *trans* addition of bromine during bromination. After the addition of one atom of bromine, the most favoured configuration is assumed

and finally the second atom of bromine is added, and whether *cis* or *trans* addition occurs depends entirely on the stable configuration of monobrom addition product.

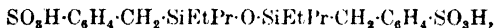
## B. Silicon

Silicon is the element most closely allied to carbon, and hence numerous attempts have been made to prepare optically active silicon compounds containing an asymmetric silicon atom, and *Kipping* and his co-workers have achieved this in several cases, e.g. *ethyl-propyl-benzyl-phenyl-silicane* (J. C. S., 1907, 209),

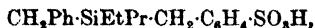


from silicon tetrachloride  $\text{SiCl}_4$  by stepwise replacement of Cl by alkyl groups with the aid of the *Grignard* compounds  $\text{EtMgBr}$ ,  $\text{PhMgBr}$ ,  $\text{PiMgBr}$ , and  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{MgBr}$ .

On sulphonation benzene is eliminated and the disulphonic acid,



**sulphobenzylethylpropylsilicyl oxide** formed. As this compound contains two similar asymmetric silicon atoms, it should give the same number of stereoisomerides as tartaric acid (p. 286). One of the acids was shown to be a *d-l*-compound, and its salt with the active base, *d*-methylhydrindamine was resolved into its optically active components when repeatedly crystallized from acetone or aqueous methyl alcohol. The two acids have extremely low rotatory powers, e.g.  $[\alpha]_D \pm 3^\circ$  to  $4^\circ$ . Similar active compounds containing an isobutyl in place of the propyl group have been obtained; they have  $[\alpha]_D \pm 10.5^\circ$ . And a compound with a single asymmetric silicon atom has been isolated, e.g. **ethylpropyldibenzylsilicanemonosulphonic acid**,



which can be resolved into active components by means of brucine (J. C. S., 1910, 755). Most of the active silicon derivatives are characterized by the close similarity between the active and racemic forms and by the low rotatory powers, so

that it is difficult to say, in certain cases, whether resolution has been effected or not.

Probably other quadrivalent elements of group IV could yield asymmetric compounds. In the case of lead a compound  $\text{PbMeEtPrBu}$  has been isolated, but so far no optically active derivatives have been prepared (*Grüttner and Krause*, B., 1917, 202). Further, the four groups may be introduced in different order, but the final product is the same, thus indicating the equivalence of the four valencies.

## C. Nitrogen

**I. Tervalent Nitrogen Compounds.**—No optical activity has been met with in compounds of the type N a, b, c, and all attempts to resolve such compounds have proved fruitless. *Jones and Millington* have attempted to resolve benzyl-phenyl-hydrazine by means of *d*-camphor-sulphonic acid, and to resolve methylethylaniline-sulphonic acid by means of brucine. Other chemists (*Krafft, Behrend and König, Ladenburg*) have attempted to resolve benzyl-ethyl-amine, *p*-tolyl-hydrazine,  $\beta$ -benzyl-hydroxylamine, methyl-aniline, and tetrahydroquinoline by means of *d*-tartaric acid.

*Kipping and Salway* (J. C. S., 1904, 438) have adopted the method of treating a secondary amine with a racemic acid chloride, namely, *d*-*l*-benzylmethylacetyl chloride,  $\text{CHMeBz}\cdot\text{COCl}$ , and examining the substituted acid amide formed. With a true *d*-*l*-base, the following compounds should be formed: *dB dA*, *lB lA*, *dB lA*, *lB dA*, of which 1 and 2 form an enantiomorphously related pair, and 3 and 4 a similar pair. Thus the complete product would be a mixture of two racemic substituted acid amides. Experiments conducted with methyl-aniline, *p*-toluidine, phenyl-hydrazine, and benzyl-aniline gave a homogeneous product in each case. Similarly, when *p*-toluidine and benzyl-aniline are condensed with *d*-methyl-benzylacetyl chloride, no indication of the formation of isomerides is met with.

An analogous method, using *d*-hydroxymethylene camphor,

$$\text{C}_8\text{H}_{14} \begin{cases} \text{C:CH}\cdot\text{OH} \\ | \\ \text{CO} \end{cases}, \text{ which reacts with secondary amines, giving}$$

compounds containing the group  $:CH\cdot NR^1R^2$  instead of  $:CH\cdot OH$ , has been used by *Pope and Read* (J. C. S., 1909, 171; 1912, 2334).

The general conclusion to be drawn is that the centres of gravity of the three radicals, and also of the nitrogen atom itself, lie in a single plane, and the whole arrangement is the most symmetrical one possible.

On the other hand dipole moments and infra-red absorption spectra point to a non-planar distribution of the three valencies in ammonia compounds, and the failure to obtain resolution of such compounds may be due to the readiness with which a molecule Nabc undergoes optical inversion.

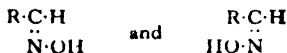
Dipole measurements indicate that the molecule of hydrazine is not planar but that the two H atoms attached to one N lie in a plane different from the one containing the other pair of hydrogen atoms (Trans. Far., 1934, 898), and hence disubstituted derivatives should exhibit stereo-isomerism (B., 1935, 1677).

**Stereochemistry of Oximes.**—The view put forward by *Hantzsch and Werner* in 1890 that the pairs of oximes derived from an aldehyde or an unsymmetrical aromatic ketone are stereo-isomeric in much the same manner as certain olefine compounds \* is still generally supported, although when introduced it was bitterly attacked, and more recently attempts have been made by *Atack* (J. C. S., 1921, 1175) to represent such pairs as structurally isomeric, e.g. three definite entities,

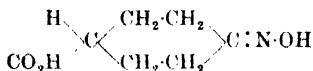
$RR'C:N\cdot OH$ , oxime proper;  $RR'C \begin{matrix} \nearrow NH \\ | \\ O \end{matrix}$  iso-oxime, and  $RR'C:NH:O$  nitron.

The reasons for retaining the stereochemical formulæ are: (1) No purely structural formula can account for the failure to obtain two isomeric oximes from a symmetrical ketone. (2) The stereochemical theory is the only one which will account for the formation of two isomeric methyl ethers, which undoubtedly exist (cf. *Brady and Dunn*, J. C. S., 1924, 291). (3) The formation of an optically active oxime (*Mills and Bain*,

\* The third valency of the nitrogen atom lies in a plane different from that of the  $\cdot N\cdot$ , and the OH of the  $:N\cdot OH$  group can have two different positions, giving rise to the two stereoisomerides represented by the projections

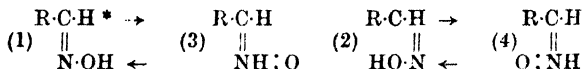


1910, 1866) of cyclohexanone-4-carboxylic acid (this Chap., A3),



Such stereochemical formulæ do not admit of the formation of N-ethers which have been proved to exist, and hence the possibility of structural as well as stereo-isomerism must be admitted. The case of the oximes of *p*-nitrobenzophenone has been studied in detail (*Brady and Mehta*, 1924, 587). Two oximes are known: (a) m.-pt. 158° and (b) m.-pt. 115°, two O-ethers melting at 93° and 96°, and two N-ethers melting at 147° and 176° are also known. Compound (a) gives the 93° and 147° ethers, and compound (b) the 96°, 147°, and 176° ethers.

It is now generally accepted that the two forms frequently isolated are stereoisomerides 1 and 2, but that each of these can react in tautomeric forms, viz. 3 or 4 which again are stereo-isomeric. These latter forms, *nitron* forms, as a rule cannot be isolated except as ethers. The third structural isomer, viz. iso-oxime, with a cyclic structure is a mobile tautomeric form of the nitron or oxime structure (cf. *Brady and Dunn*, 1916, 659; *Plowman and Whiteley*, 1924, 587; *Griffiths and Ingold*, 1925, 1698).



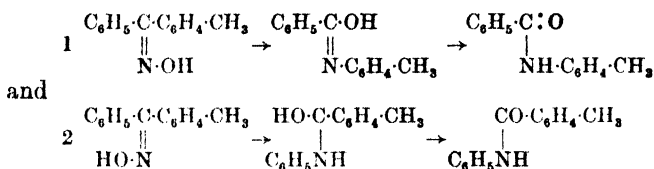
*Meisenheimer, Lange and Lamparter*, A., 1925, **444**, 94, have actually isolated four distinct *p*-methoxybenzil-mon-oximes.

**Determination of Configuration.**†—The method adopted by *Hantzsch* in the case of aldoximes was to treat the two isomerides with acetyl chloride, the one which readily lost water yielding a nitrile ( $\text{CH:N}\cdot\text{OH} \rightarrow \text{C:N}$ ) was given the *syn* or *cis* configuration 1, and the one which yielded a stable acetyl derivative was given the *anti* or *trans* configuration 2.

Again, in the case of stereo-isomeric ketoximes an examination was made of the products formed by the *Beckmann* transformation under the influence of acetyl chloride. It was

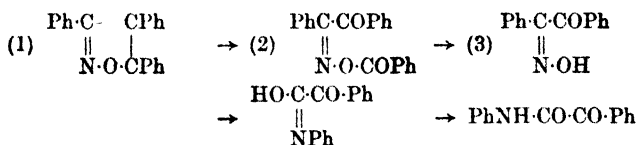
\* Or R'. † Beckmann Rearrangement, *Chem. Rev.*, 1933, 215.

assumed that in this transformation *cis* exchange of groups occurs, e.g.:

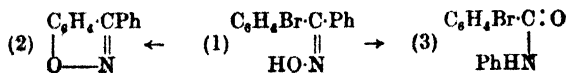


the isomer which yields the toluidide of benzoic acid would have configuration 1, and the one yielding the anilide of toluic acid configuration 2.

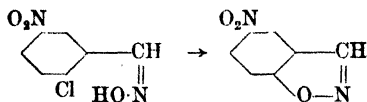
Both these methods have been abandoned as reliable tests for configurations. It has been pointed out that they are based entirely on the idea of *cis* elimination and *cis* exchange. It has been proved beyond doubt that frequently in passing from an olefine derivative to an acetylene *trans* elimination occurs (p. 282), and similarly *trans* addition to an acetylene compound often occurs. It is now generally accepted that in nitrile formation from an oxime *trans* elimination takes place, and that in the *Beckmann* transformation *trans* exchange is the rule. This change of view has been largely brought about by a study of the relationships of oximes to cyclic structures, more particularly the benzisooxazoles. *Meisenheimer* (B., 1921, 3206) was able to show that the fission of triphenylisooxazole (1) with ozone gives a benzoyl derivative of benzil monoxime (2); and the oxime itself (3) subjected to the *Beckmann* rearrangement gives  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{CO}\cdot\text{CO}\cdot\text{C}_6\text{H}_5$



Again, with the *o*-chloro- and *o*-bromo-benzophenone oximes (B., 1924, 289) the compounds (1) which readily lose halogen hydracid yielding benzisooxazole (2) are those which yield anilides of *o*-chloro- and *o*-bromo-benzoic acid (3).

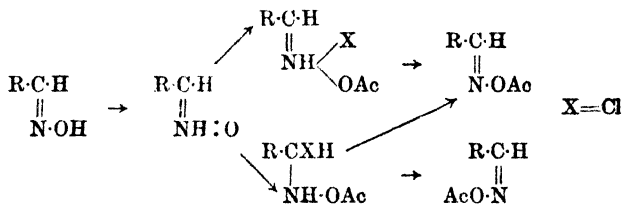


A similar argument can be used in the case of 2-chloro-5-nitrobenzaloxime, the form



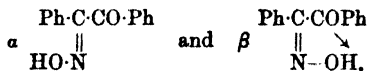
which yields the nitrobenzisooxazole is the one in which H and OH are in *trans*- or *anti*-positions, i.e. the H of the OH and Cl of the benzene ring are vicinal. (For examples and discussion cf. *Brady and Bishop*, J. C. S., 1925, 1357; *Beckmann*, *Liesch and Correns*, B., 1923, 341; *Auwers and Oltens*, 1924, 446.)

*Brady and McHugh* (1925, 2414) have examined the inter-conversion of the geometrical isomerides by acylating 16 aldoximes with 8 different acylating agents, and suggest that the change of configuration of one oxime into the other can be best accounted for by assuming the intervention of the nitron form and the addition of the acylating agent, e.g.  $\text{CH}_3\cdot\text{CO}\cdot\text{Cl}$ , to this form in two different ways:



For conductivities of stereo-isomeric oximes see *Brady*, J. C. S., 1929, 946, and for ether formation, 1926, 2403; 1929, 2271.

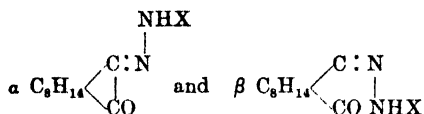
The formulæ,



for the benzil monoximes melting respectively at  $134^\circ$  and  $113^\circ$  based on the study of iso-oxazole formation have been recently confirmed by a study of physical properties, e.g. solubility and volatility (*Taylor and Ewebank*, J. C. S., 1926, 2818). In the  $\beta$ -compound probably there is a co-ordinate link between O of CO and H of OH (cf. *Sidgwick*, 1925, 907).

The phenylhydrazones derived from unsymmetrical ketones

often exist in two forms which are generally regarded as stereo-isomeric in the same manner as a pair of oximes, the :N·NHP<sub>h</sub> replacing the :N·OH grouping. The determination of configuration is again usually based on the ease with which ring closure can occur. The method was first used by *Foster and Zimmerli* (J. C. S., 1910, 2156) for camphorquinone phenylhydrazones and semicarbazones:

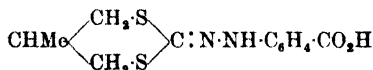


as the  $\beta$ -compounds, e.g. semicarbazone where X = ·CO·NH<sub>2</sub>

readily form a cyclic oxytriazine,  $\text{C}_6\text{H}_5 \begin{array}{c} \diagup \text{C} \cdot \text{N} \cdot \text{NH} \\ \diagdown \text{C} \cdot \text{N} \cdot \text{CO} \end{array}$

A similar method has been used in other cases (cf. *Busch* and others, B., 1924, 1783).

The compound



is also resolvable.

**Azobenzene** (Chap. XXII, C.) exists in two stereo-isomeric forms, the ordinary compound, b.-pt. 68°, is the *trans* form I and a new compound, m.-pt. 71°–74°, is the *cis*-compound II,



Both have same molecular weight, but the *cis* has a distinct dipole moment and is more soluble. An equilibrium mixture of the two is formed on exposing solutions to light, and the composition of the equilibrium mixture varies from 15–40 per cent of *cis* according to the solvent (J. C. S., 1938, 633; 1939, 232).

**Quinquevalent Nitrogen Compounds.**—(For formation see pp. 116, 441.) The most interesting type of compound is that in which all five radicals are different, e.g. N a, b, c, d, X. These compounds are quaternary ammonium salts, in which four of the radicals are alkyl groups, and the fifth an acid group. No cases of inactive isomerides have been met with. An example described by *Wedekind*, viz. methylallylphenylbenzylammonium iodide, has been shown by *H. O. Jones* (J. C. S., 1905, 1721) to be non-existent.

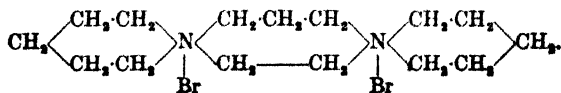


The only known examples of stereoisomerides are the optically active modifications in which compounds of the type **methylethylpropylisobutylammonium chloride**,  $N(CH_3)(C_2H_5)(C_3H_7)(C_4H_9)Cl$ , exist. This type of compound is always obtained in an inactive form when synthesized in the laboratory by the addition of an alkyl haloid to a tertiary amine. In 1891 *Le Bel* claimed to have obtained a *lævo*-modification by means of *Penicillium glaucum* (green mould), and in 1899 he confirmed this result. In the same year *Pope* and *Peachey* (J. C. S., 1899, 1127) obtained a resolution of *Wedekind's* benzylphenylallylmethylammoniumiodide by the aid of silver *d*-camphor-sulphonate.

When the mixture of **benzylphenylallylmethylammonium d-camphor-sulphonates** is crystallized from acetone, a sparingly soluble fraction is obtained, and this, when treated with potassium iodide, yields an optically active iodide,  $N(C_7H_7)(C_6H_5)(C_3H_5)(CH_3)I$ , with  $[M]_D + 192^\circ$ .

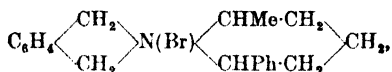
*H. O. Jones* (J. C. S., 1903, 1418; 1904, 223) resolved phenylbenzylmethylethylammonium iodide and phenylmethylethylallylammonium iodide by means of silver *d*-bromo-camphor-sulphonate, and also observed that many of these salts show a tendency to undergo racemization. During the fractional crystallization of the salts it is advisable to keep the temperature as low as possible. Auto-racemization (p. 294) occurs when the cold chloroform solutions are kept in the dark, a phenomenon also observed by *Pope* and *Harvey* (J. C. S., 1901, 828) with other optically active ammonium salts, and probably due to a partial dissociation of the quaternary ammonium salt into tertiary amine and alkyl iodide and subsequent recombination.

Quinquevalent nitrogen derivatives of the type  $Na_2bcX$ , e.g. phenylallyldimethylammonium iodide, phenyldipropylmethylammonium iodide, &c., do not exist in isomeric modifications, and attempts to resolve such compounds into optically active components have given negative results (J. C. S., 1897, 522; 1903, 1141, 1406; 1904, 412). *Aschan* (Zeit. phys. 1903, 46, 304) has prepared isomeric spiran nitrogen compounds containing two quinquevalent nitrogen atoms, viz.:

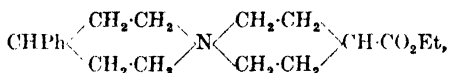


The one compound is formed by the union of ethylene-dipiperidine with trimethylene bromide, and the other by the combination of trimethylene-dipiperidine with ethylene bromide. This isomerism can be accounted for if the bromine atoms and the central ring lie in one plane and the other rings in a plane at right angles to the first.

Similar compounds containing one nitrogen atom,



exist in two forms (*Scholz*; B., 1910, 2121), and the compound



4-phenyl-4'-carbethoxy-bispiperidinium-1 : 1'-spiran, is also resolvable (1935).

Methylethylaniline oxide,  $\text{NPhMeEtO}$ , has been resolved into active modifications by means of bromocamphorsulphonic acid. The base itself, probably  $\text{NPhMeEt}(\text{OH})_2$ , has  $[\alpha]_D - 25^\circ$  (*Meisenheimer*, A., 1911, 385, 117).

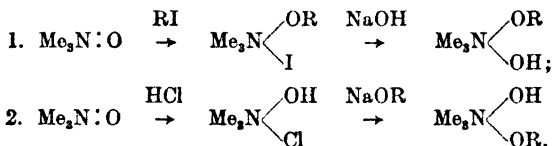
The compound,  $\text{I} \cdot \text{NMeEtPh} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NMeEtPhI}$ , containing two similar asymmetric nitrogen atoms, like tartaric acid, exists in two inactive forms but so far neither has been resolved into active components. The compound,  $\text{I} \cdot \text{NMePh}(\text{C}_3\text{H}_5) \cdot \text{CH}_2\text{CH}_2 \cdot \text{CH}_2 \cdot \text{NMePhBz} \cdot \text{I}$ , contains two dissimilar asymmetric nitrogen atoms, and should resemble cinnamic acid dibromide, and exist in two pairs of enantiomorphous compounds. In reality two inactive forms have been isolated, but so far both have resisted all attempts at resolution (*Wedekind*, B., 1910, 2707; 1916, 942). When an asymmetric nitrogen atom is introduced into an active compound already containing an asymmetric carbon atom, two active stereoisomerides, which are not optical antipodes, are formed, just as two products are formed when a new asymmetric carbon atom is introduced into an optically active carbon compound.

An interesting case of the existence of four stereo-isomeric compounds of the type,  $\text{abC} : \text{N} : \text{N} : \text{Ccd}$ , has been demonstrated, viz. with the compound,  $\text{CHPh} : \text{N} : \text{N} : \text{C}(\text{SMe}) \cdot \text{S} \cdot \text{CH}_3$ ,

$\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2$  (Busch, J. pr., 1916, **93**, 25). The four possibilities are:

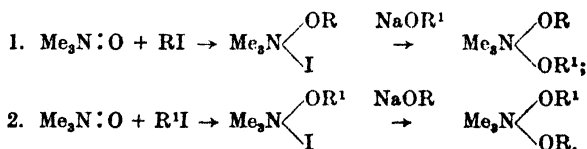


*Meisenheimer* (A., 1913, **397**, 273) claims to have proved the non-equivalence of the five valencies of the quinquivalent nitrogen atom by the following series of reactions, starting with trimethylamine oxide (p. 123):



As far as could be ascertained, the final products in the two reactions were not identical but isomeric, as the solution of the first compound when evaporated yielded trimethylamine, an aldehyde, and water, whereas the product from the second series of reactions under similar treatment gave trimethylamine oxide and the alcohol  $\text{R}\cdot\text{OH}$ . In a similar manner

isomeric compounds  $\text{NMe}_3 \begin{array}{l} \text{OR} \\ \text{OR}^1 \end{array}$  have been prepared by the following series of reactions:



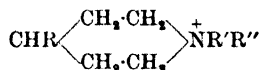
Compare also A., 1913, **399**, 366, 371, 377.

Various suggestions for the spatial arrangement of the five groups around the quinquivalent nitrogen atom have been made, e.g. *Bischoff* represented the nitrogen at the centre of a pyramid on a rectangular base with the 5 groups at the solid angles, and *Willgerodt* a similar arrangement but with a double pyramid on a triangular base. The recognition of ions and their existence even in the crystalline state as demonstrated by X-ray analysis has afforded a simple explanation of the stereochemistry of quinquivalent nitrogen.

It is the ammonium cation, with its four alkyl or substituted alkyl groups, which exhibits activity, and it is now generally recognized that the spatial arrangements of such an ion are tetrahedral just as in the case of quadrivalent carbon, and this arrangement was first suggested by *H. O. Jones* and *Dunlop* (*J. C. S.*, 1912, **101**, 1751; cf. *Meisenheimer*, *A.*, 1913, **397**, 300; *Komatsu*, *Abs.*, 1918, i, 426; *Neogi*, *J. A. C. S.*, 1919, 622).

Such a tetrahedral arrangement is in complete harmony with the following results, which have been established by experiment:

1. The non-equivalence of the fifth valency.
2. The non-existence of isomerides of the types  $\text{Na}_3\text{bX}$  and  $\text{Na}_2\text{bcX}$ .
3. The existence of two enantiomorphous isomerides  $\text{NabcdX}$ .
4. The existence of four active isomerides of the type  $\text{Cabc}\cdot\text{NabcX}$ .
5. The existence of 4-phenyl-1-methyl-1-ethylpiperidonium iodide or generally of salts derived from the ion



in two non-resolvable stereo-isomeric (*cis* and *trans*) forms (*Mills, Parkin and Ward*, *J. C. S.*, 1927, 2613, cf. 1925, 2507). If the ammonium ion has the tetrahedral configuration the compounds of this type should resemble the cyclohexane-1:4-dicarboxylic acids (Chap. XVI), and exist as *cis* and *trans* isomerides, both of which should be of the non-resolvable type, and this isomerism should disappear in all cases where  $\text{R}' = \text{R}''$ . On the other hand, with a pyramidal configuration of the ammonium ion when  $\text{R} = \text{R}'$  two non-resolvable forms should exist and when  $\text{R}'$  differs from  $\text{R}''$  two racemic forms. By an examination of five different compounds of this type, three in which  $\text{R}'$  and  $\text{R}''$  were different, and two in which they were identical, it was found that all the facts pointed to the tetrahedral structure.

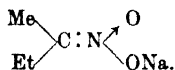
6. The resolution of the salts of amine oxides. These may be represented as containing the ion  $\text{Nabc}(\text{OH})^+$  or in the  $\equiv\text{N}:\text{O}$  group the double linking between O and N may be semipolar (*Meisenheimer* and others, *A.*, 1926, **449**, 188).

The discovery of compounds in which nitrogen is attached

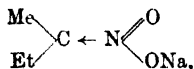
to five hydrocarbon groups, e.g. tetramethylbenzylammonium,  $\text{NMe}_4\cdot\text{CH}_2\cdot\text{Ph}$  (p. 442), does not render the tetrahedral arrangement untenable, as in these compounds one of the five groups appears to occupy a characteristic position with respect to the nitrogen. It has been shown that solutions of such compounds in pyridine are electrolytes, and hence one of the alkyl groups is presumably ionizable as an anion in the same manner as the halogen atom in quaternary ammonium salts.

### 3. OPTICALLY ACTIVE ALIPHATIC NITRO-COMPOUNDS

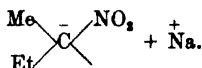
By starting with the optically active alcohol,  $\text{MeEtCH}\cdot\text{OH}$ , *Kuhn* and *Albrecht* (B., 1927, 1297) obtained an active methyl-ethylnitromethane,  $\text{MeEt}\cdot\text{CH}\cdot\text{NO}_2$ , the ionizable sodium salt of which according to *Hantzsch* should be represented as:



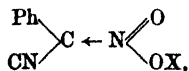
These structures are symmetrical, and hence the compounds should not be optically active and the alternative structure,



has been suggested, where the co-ordinate link is between C and N, the N being the donor, or possibly



A similar compound with  $\text{C}_6\text{H}_{13}$  in place of  $\text{C}_2\text{H}_5$ , i.e. an optically active nitro-octane, has been obtained by *Shriner* and *Young* (J. A. C. S., 1930, 3332), and *Mills* and *Cole* (1932) have resolved phenylcyanonitromethane,  $\text{CN}\cdot\text{CHPh}\cdot\text{NO}_2$ , by means of its brucine salt with the structure

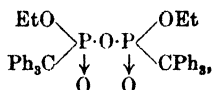


and it is thus clear that optical activity occurs with compounds containing a co-ordinated carbon atom,  $>\text{C} \leftarrow$  as the centre of dissymmetry. The potassium salt of 2-bromo-9-nitrofluorene (J. A. C. S., 1935, 2163) is also slightly active.

### D. Phosphorus and Arsenic

*Meisenheimer* and *Lichtenstadt* (B., 1911, 356) have obtained methylethylphenylphosphine oxide,  $\text{O:PMeEtPh}$ , in optically active forms. The base was prepared by combining methyl iodide with ethyldiphenylphosphine, liberating the base with moist silver oxide and then distilling, and was resolved by means of *d*-bromo-camphor-sulphonic acid. The base has  $[\alpha]_D + 33.8$  in benzene solution. Somewhat similar experiments of *Caven* (J. C. S., 1902, 1362) and *Ephraim* (B., 1911, 631) have given negative results.

**Ethyl triphenylmethyl-pyro-phosphate,**



exists in meso and racemic forms, but both give the same acid on hydrolysis owing to resonance (J. C. S., 1933, 776).

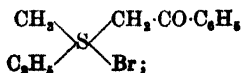
Arsenic compounds, e.g. phenyl- $\alpha$ -naphthylbenzylmethylarsonium iodide (*Burrows* and *Turner*, J. C. S., 1921, 426) and *p*-carboxyphenylmethylethylarsine sulphide,  $\text{CO}_2\text{H} \cdot \text{C}_6\text{H}_4 \cdot$

As  $\begin{array}{c} \text{S} \\ \swarrow \quad \searrow \\ \text{Me} \quad \text{Et} \end{array}$  (*Mills* and *Raper*, 1925, 2479), have been resolved.

For more complex compounds see *McClelland* and *Whitworth* (1927, 2753).

### E. Sulphur, Selenium and Tin

As sulphur, selenium and tin can function as quadrivalent elements, *Pope*, with *Peachey* and *Neville* (1900-2), examined compounds of these elements in which the central atom is attached to four different monovalent groups, and found that compounds of the types: (a) **Methylethylthetine bromide**,  $\text{Br} \cdot \text{SMeEt} \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$ , obtained by the addition of bromoacetic acid to methylethyl sulphide; (b) **Methylethylphenacylsulphine bromide** (*Smiles*, J. C. S., 1900, 1174):



(c) **Methylethylselenetine bromide**,  $\text{SeMeEtBr}\cdot\text{CH}_3\cdot\text{CO}_2\text{H}$ , obtained from methylethyl selenide and bromo-acetic acid; (d) **Phenyl-*p*-tolyl-methyltelluronium iodide**,  $\text{TeMePhC}_7\text{H}_7\text{I}$  (*Lowry and Gilbert*, J. C. S., 1929, 2868); (e) **Methylethylpropyl-tin iodide**,  $\text{I}\cdot\text{SnMeEtPr}$  (a liquid boiling at  $270^\circ$ ), were all resolved by treating with silver *d*-camphor-sulphonate or silver *d*-bromocamphor-sulphonate, removing the silver halide and repeated crystallization of the salts when the least soluble salt could be obtained pure. In most cases racemization readily takes place, and in the case of the tin compounds the following phenomena were observed.

Crystals of *d*-methylethyl-*n*-propyl-tin *d*-camphor-sulphonate,  $\text{SnMeEtPr}\cdot\text{O}\cdot\text{SO}_2\cdot\text{C}_{10}\text{H}_{15}\text{O}$ , melting at  $125^\circ\text{--}126^\circ$ , were obtained. In aqueous solution  $[\text{M}]_D = +95^\circ$ , which gives a value for the univalent ion,  $\text{SnMeEtPr}$ , of about  $+45^\circ$ . When the mother liquor from the above-mentioned crystals was evaporated, a further quantity of the same compound was obtained, and the operation repeated until all the water had been expelled. No trace of *l*-methylethylpropyl-tin *d*-camphor-sulphonate could be isolated. *Pope and Peachey* attribute this to the conversion of the *l*-base into the *d*-base by continued racemization (p. 293), in the following manner: The solution of the racemic base with the *d*-acid deposits a portion of its *d*-base as the sparingly soluble salt *d*-base + *d*-acid; the excess of *l*- over *d*-base remaining in the solution racemizes as evaporation proceeds, a further quantity of *d*-base separates as salt, and racemization of the residue again proceeds.

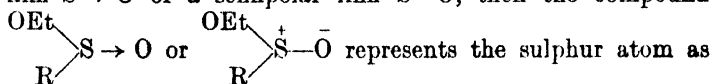
For other examples of the same type cf. *King*, Rep., 1933, 261.

All the compounds investigated are salts, and the activity of a halide is due to the cation containing, e.g.,  $\text{SnMeEtPr}^+$ , i.e. tervalent derivatives of S, Se and Sn. It is clear, therefore, that the spatial arrangements in these ions must be different from that in tervalent nitrogen compounds, and it may be that the S (Se or Sn) atom occupies one corner of a tetrahedron and the three alkyl groups the remaining three corners.

Just as the amine oxides  $\text{Nabc}\cdot\text{O}^+$  or  $\text{Nabc}\cdot\text{OH}^+$  exist in enantiomorphous forms, so do the sulfoxides  $\text{O}\cdot\text{SRR}'$  (*Harrison, Kenyon, and Phillips*, J. C. S., 1926, 2079), and sulphinates

$\text{R}\cdot\text{S}\begin{array}{l} \diagup \text{O} \\ \diagdown \text{OEt} \end{array}$  (*Phillips*, J. C. S., 1925, 2552). The existence of

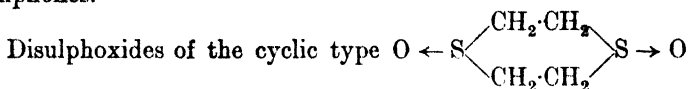
such stereoisomerides is not explicable with the usual structural formula, but representing the S:O linking as a co-ordinate link  $S \rightarrow O$  or a semipolar link  $\overset{+}{S}-\bar{O}$ , then the compound



attached by three single linkings to three different groups; in other words, the arrangement in the optically active thionium ion described above. The compounds actually resolved were *p*-toluene sulphinate, *p*-tolyl-*p*-aminophenyl sulphoxide and *m*-carboxyphenylmethyl sulphoxide and still later a sul-

philimine,  $\text{C}_6\text{H}_4 \cdot \text{SO}_2 \cdot \bar{\text{N}} - \overset{+}{\text{S}} \begin{array}{l} \diagup \text{C}_6\text{H}_4\text{CO}_2\text{H} \\ \diagdown \text{CH}_3 \end{array}$ , obtained by condens-

ing chloramine T with *m*-carboxyphenyl methyl sulphide (J. C. S., 1927, 188), by means of brucine or cinchonidine. Optical activity disappears when the active sulphinates and sulphoxides are oxidized respectively to sulphonates and sulphones.

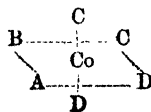
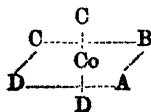


exist in two inactive stereo-isomeric forms (Bell and Bennett, J. C. S., 1927, 1798; 1928, 86), which can be accounted for on the semipolar double bond basis, and the two oxygen atoms can be *cis* or *trans* to the plane of the carbon and sulphur

atoms, and also oxides of the type  $\text{O} \leftarrow \text{S} \begin{array}{c} \diagup \text{CH}_2 \cdot \text{CH}_2 \\ \diagdown \text{CH}_2 \cdot \text{CH}_2 \end{array} \text{Cab}$  (J. C. S., 1929, 2832; 1930, 1).

## F. Co-ordination Compounds

In 1911 *Werner* pointed out that compounds of the types  $\text{CoA}_3\text{BCD}$  and  $\text{CoABC}_2\text{D}_2$  should exist in two optically active isomerides provided the groups ABCD are arranged spatially, i.e. octahedrally, around the central Co atom:





and active isomerides were actually isolated in the case of the bromo-ammine-diethylenediamine cobalt salts,\*  $[\text{CoBrNH}_3\text{en}_2]\text{Br}_2$ , the resolution being accomplished with the aid of *d*-bromocamphor-sulphonic acid, and similar results were obtained with chromium co-ordinated salts (B., 1911, 2445, 3279, 3722, 3132). When an unsymmetrical diamine, e.g.  $\text{NH}_2\text{-CH}_2\text{CHR-NH}_2$ , takes the place of DD or a sym. diamine that of CC, and  $\text{A} = \text{B}$ , two series of compounds exist (Helv., 1919, 5).

Since *Werner's* results were made known an enormous number of co-ordinate complexes derived from other elements have been isolated, and it is possible to classify these compounds into the categories according to the arrangements of the groups around the central atom:

1. Planar: elements with co-ordinate number 4.
2. Tetrahedral: elements with co-ordinate numbers 3 or 4.
3. Octahedral: elements with co-ordinate number 6.

Under group 1 fall certain compounds derived from Ni, Pd, Pt, and Au. The groups and the central atom lie in a single plane and the compounds are not resolvable into optically active components.

Under group 2 are derivatives of Be, B, C, N, Si, P, S, Se, Cu, Zn, As, Sn, Ag, Te. The arrangement is exactly analogous to that of compounds with an asymmetric carbon atom. The compounds are resolvable.

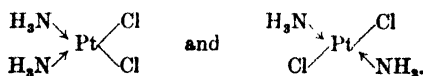
Under group 3 are compounds of Al, Cr, Fe, Co, Ni, Cu, As, Ph, Pt.

Thus the elements Ni, Cu, As, Pt can give derivatives belonging to two different types of grouping.

The determination of the spatial structure is largely based on the following considerations:

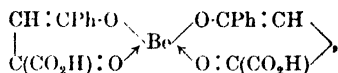
1. The existence of two distinct isomerides which cannot be resolved into active components.

The compound  $\text{PtCl}_2\text{2NH}_3$  exists in two non-resolvable isomeric forms, which therefore have a planar structure and can be represented as



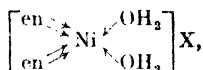
\* Where en represents the twofold associating group ethylenediamine which is thus equivalent to two D groups (cf. Chap. XLVI, A.).

2. The resolution of the compound into optically active isomerides just as in the case of carbon compounds. Thus the beryllium-benzoyl-pyruvic acid and the corresponding Zn and Cu compounds exist in optically active forms and hence have the tetrahedral configuration:



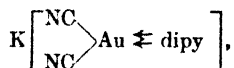
where the 4 links of the beryllium atom are directed towards the angles of a tetrahedron. The compounds are not beryllium salts as they are not ionizable, they have low melting-points, volatilize without decomposition and dissolve readily in hydrocarbon solvents (*Mills and Gotts*, J. C. S., 1926, 3132).

Similar complex nickel salts, e.g. the bisethylenediamine salts (*Wahl*, 1928),



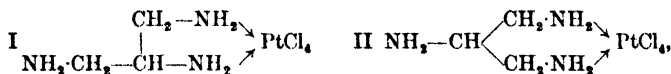
and the tris- $\alpha$ -dipyridyl salts  $[\text{N3 dipy}]\text{Cl}_2$  (*Morgan and Birstall*, J. C. S., 1931, 2213) are resolvable and hence have the octahedral structure.

The gold compound,



is coplanar and not tetrahedral, and in it the gold has the stable radon electron structure (J. C. S., 1939, 426).

An interesting compound is that of  $\text{PtCl}_4$  with 1:2:3-triaminopropane. This can yield the 5-ring compound I or the 6-ring compound II,



and as the compound is resolvable I is probably correct.

*Vernon* (1920-21) claimed to have isolated two isomeric  $\text{TeMe}_2\text{I}_2$  and hence deduced a planar configuration. *Drew* (J. C. S., 1929, 560) proved that one of these was the polymer  $\text{Te}_2\text{Me}_4\text{I}_4$  and a true salt, and finally *Lowry and Gilbert* (1929, 2867) resolved the phenyl-*p*-tolyl-methyl-telluronium salts

and thus proved the telluronium ion to have the tetrahedral arrangement.

3. X-ray examinations can be of use in deciding the configurations of molecules in the solid and vapour phases. When applied to a compound of the type  $[\text{Pt}4\text{NH}_3]\text{Cl}_2$  it shows that the 4 groups attached to the platinum atom lie in the same plane as the Pt atom itself (Cox, 1932, 1912), and probably other platinum compounds with a co-ordinate number 4 have the same planar structure.

4. A study of infra-red spectra or of *Raman* effects throws light on magnitudes of moments of inertia and hence on configurations.

The accumulated evidence shows that with an atom with the co-ordinate number 4, or with a 4 covalent atom with single links, the structure is usually tetrahedral but occasionally planar, but with atoms with a co-ordinate number 6 the configuration is invariably octahedral.

The formation of a chelate ring always enhances the stability of a co-ordinated compound as shown by the relative stability of the complexes formed by aliphatic amines on the one hand and ethylene and propylene diamines on the other, but as chelate rings are usually 5- or 6-membered rings a diamine such as decamethylene-diamine which cannot form a chelate ring with the metal yields very unstable co-ordinated compounds (cf. Diehl, Chem. Rev., 1937, 39). For a list of co-ordinating power of some of the more common donor groups, e.g. cyanide aliphatic amine, pyridine bases, unsaturated hydrocarbons, amino-acids and *d*-tartaric acid with different metals, cf. Bailhar, *ibid.* 1938, 71.

For co-ordination of unsaturated carbon compounds see Anderson, J. C. S., 1934, 971; 1936, 1042; Kharasch and Ashford, J. A. C. S., 1936, 1733.

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## LI. UNSATURATION \*

## A. Types of Unsaturation

The term unsaturated has been frequently applied in earlier chapters to different compounds without any clear definition of the term. It has been used to comprise all cases of compounds which are capable of uniting with other elements or compounds, thus olefines with bromine or hydrogen, aldehydes with hydrogen cyanide or bisulphites. The best definition is "Unsaturated compounds are those capable of uniting with another substance (element or compound) without a disruption of their original structure". Two main types may be distinguished.

## 1. TWO ADDENDA ATTACHED TO THE SAME ATOM

Cases in which the addenda unite with one and the same atom of the original compound, as in the conversion of amines into salts and quaternary ammonium compounds, the formation of oxonium salts from ethers, &c., and the formation of sulphonium salts from alkyl sulphides.

The presence of such unsaturated groups as amino and hydroxyl, and also the alkylated groups,  $\cdot\text{NHR}$ ,  $\cdot\text{NR}_2$ ,  $\cdot\text{OR}$ , produce marked effects on the properties of the compounds into which they are introduced. In the aromatic series they render the compounds much more reactive towards reducing, oxidizing, and substituting reagents (cf. p. 472). When further substituents are introduced, e.g.  $\text{Cl}$ ,  $\text{Br}$ ,  $\text{SO}_3\text{H}$ ,  $\text{NO}_2$ , &c., these almost invariably take the ortho- and para-positions with respect to the unsaturated group. These groups also tend to make the compound luminesce under the influence of electric discharges under small pressures. They are also the most powerful *auxochromes* known, i.e. when introduced into a compound containing chromophores, such as  $\cdot\text{N}:\text{N}$ ,  $\text{C}:\text{O}$ ,  $\text{C}:\text{C}$ ,  $\text{NO}_2$ , &c., they produce a deepening of the colour of the compound.

In each case the atom involved passes to a higher valency state, e.g. from 2 to 4 or 3 to 5, and in practically all cases the

\* For theoretical views cf. E. Hückel, "Grundzüge der Theorie ungesättigter und aromatischer Verbindungen", Z. elec., 1937, 752 and 785.

product formed is an ionizable salt, i.e. the element in question with its attached groups acts as a cation. Thus trimethylamine and methyl iodide ( $\text{Me}$ ,  $\text{I}$ ) yield  $\text{NMe}_4^+$ ,  $\text{I}^-$ , the positive charge of the  $\text{Me}$  is transferred to  $\text{N}$ .

**Salt Formation in Case of Cyclic Oxygen Compounds.**—

This has been studied in the case of pyrones and similar compounds (*B. W. Ghosh*, *J. C. S.*, 1915, 1588) by means of perchloric acid. Many ring compounds containing one or two atoms of oxygen do not form oxonium salts with perchloric

acid, e.g.  $\text{O} \begin{array}{c} \text{CH}_2\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_2\text{CH}_2 \end{array} \text{CH}_2$ ,  $\text{O} \begin{array}{c} \text{CH}_2\text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CH}_2\text{CH}_2 \end{array} \text{O}$ , and the corre-

sponding compounds condensed with a benzene nucleus. The introduction of olefine linkings, the replacement of  $\text{CH}_2$  by  $\text{CO}$ , or an accumulation of benzene nuclei increases the basic properties of the oxygen and facilitates salt formation.

An attempt to settle the structure of salts of simple unsymmetrical  $\gamma$ -pyrones has been made by *Gibson and Simonsen* (*J. C. S.*, 1928, 2307) by trying to isolate two 2-methyl-6-phenyl-4-pyrone *d*- $\alpha$ -bromocamphor-sulphonates. No isomerides could be detected, and they consider this favours the *pyrylium* structure I rather than the ordinary oxonium formula II, (p. 679).



The pyrylium structure is met with in many anthocyanidins (*Chap. LXIV, C*).

**Molecular Compounds.**—Analogous to the unstable oxonium salts are the additive compounds formed by the union of aromatic compounds, more particularly amines, phenols, and phenolic ethers with quinones and aromatic nitro-compounds of the type of *s*-trinitrobenzene, polynitronaphthalenes, and even *m*-dinitrobenzene. Many of these compounds are highly coloured, and similar products are given by hydrocarbons containing condensed benzene nuclei, e.g. anthracene, phenanthrene, fluorene, &c. (*Pfeiffer*, "Organische Molekülverbindungen", 2nd Edition, 1927; *Bennett and Willis*, *J. C. S.*, 1929, 256, who give electronic formulæ for such compounds and for general discussion; see *C. and I.*, 1938, 512.)

*Hammick* and others (*J. C. S.*, 1936, 1463; 1938, 764, 1350) by a study of the effects of increasing amounts of solvent on

the colour of the compounds of amines with trinitrobenzene show that the stability is largely a function of the strength of the base.

## 2. TWO ADDENDA ATTACHED TO TWO DIFFERENT ATOMS

The addenda become attached to two different atoms, which may be (a) adjacent atoms, (b) atoms removed from one another by a chain of one or more atoms. Type (b) is not very common, and the best-known example is the addition of bromine to cyclopropane accompanied by the breaking of the tri-ring and the formation of the open-chain compound, trimethylene bromide,  $\text{CH}_2\text{Br}\cdot\text{CH}_2\cdot\text{CH}_2\text{Br}$ .

The common type is (a), e.g. the addition of 2H to ethylene to form ethane, or of bromine to oleic acid to form 9 : 10-dibromo-stearic acid.

It has been definitely proved in the case of ethylene dibromide that the bromine atoms are attached to different carbon atoms (p. 67) and somewhat similar arguments can be used in other cases.

Compounds of type (a) are usually represented as containing double or triple linking between the two adjacent atoms, e.g.  $\text{C}:\text{C}$ ,  $\text{C}:\text{N}$ ,  $\text{C}:\text{O}$ ,  $\text{C}:\text{S}$ ,  $\text{S}:\text{O}$ ,  $\text{N}:\text{N}$ ,  $\text{C}:\text{C}$ ,  $\text{C}:\text{N}$ , &c. This merely means that all the valencies which are not used up in attaching H or other element or group to C, O, or N are used up in attaching C to C, C to O, C to N, or in other words when there are not enough electrons in a molecule to provide each atom with its stable octet by formation of single covalent links, two adjacent atoms may share a second or even a third pair of electrons. This is limited, however, to C, N and O. With S and P and other elements co-ordinate links are usually formed.

A double or triple bond in a carbon compound is not a strengthened bond as it should be if each link in a double bond was the equivalent of a single bond. Characteristics of olefine compounds are (i) their high energy content as illustrated by their heats of formation, e.g. ethane has +25.0, ethylene -6.45, and acetylene -54.4 kilo cal. per gm. mol.; (ii) a diminution in the distance between the two C atoms, e.g. 1.44 Å as compared with 1.54 from  $\text{C}-\text{C}$ ; (iii) the absorption of light of greater wave-length than compounds with single links; (iv) the double link prevents free rotation about the axis common to the two C atoms.

In terms of the electronic conception of links, a double link denotes that each of the two atoms concerned shares four electrons, two from each atom. In a simple hydrocarbon,  $\text{CH}_2:\text{CH}_2$ , it is highly probable that the two pairs of electrons are equally shared between the two carbon atoms and the compound is non-polar, but with the introduction of substituents, even  $\text{CH}_3$  or  $\text{Cl}$ , electric disturbances arise and a more or less unequal sharing of the four electrons occurs.

This may be represented as  $\overset{\curvearrowright}{\text{A}} = \text{B}$  and  $\text{A} = \overset{\curvearrowleft}{\text{B}}$ , indicating

a tendency for a displacement of an electron pair and leaving the one atom with an unstable sextet. Such active forms are extremely mobile and of very short life, so that their concentration is always small and the equilibrium is

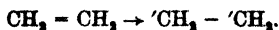


When A and B represent different elements, e.g. C and O, there is always a tendency for the atom with the higher effective nuclear charge to retain the electron pair, and hence  $\text{N} = \text{O}$  and  $\text{S} = \text{O}$  readily become  $\text{N} \rightarrow \text{O}$ ,  $\text{S} \rightarrow \text{O}$ .

Although most compounds containing double links form additive compounds they vary considerably as to the compounds with which they can combine. Thus compounds with  $\text{C}:\text{C}$  combine with  $\text{H}_2$ ,  $\text{Cl}_2$ ,  $\text{HBr}$ ,  $\text{HClO}$  readily, whereas compounds with  $\text{C}:\text{O}$  combine with  $\text{H}_2$ ,  $\text{HCN}$ ,  $\text{NaHSO}_3$  and  $\text{H}_2\text{O}$ .

## B. Mono-enes

Compounds containing one olefine link are those which have been most closely studied. The addition may be non-ionic and may be due to the symmetrical rupture of a dublet giving rise to a pair of free radicals united by a single link (cf. Free Radicals, Chap. LII, B.):



The following reactions probably belong to this type. The photochemical reduction of ethylene (*Taylor and Marshall*, J. Ph. Chem., 1925, 1140) and the addition of halogens to cinnamic acid in sunlight (*Wachholz*, Z. phys., 1927, 125, 1),

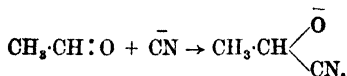
the photochemical addition of  $\text{H}_2\text{O}_2$ , i.e.  $\text{OH} + \text{OH}$ , to olefines, e.g. crotonic acid + 10 per cent perhydrol gives dihydroxybutyric acid in ultra-violet light and allyl alcohol gives glycerol (J. A. C. S., 1937, 543). The photochemical formation of phosgene,  $\text{COCl}_2$ , appears to be a non-ionic reaction and has received considerable attention (*Bodenstein*, 1927-30). The rate of change approximates nearly to the square root of the concentration of chlorine molecules, indicating that the chlorine is split into atoms. The reaction is a typical chain reaction and appears to take place in the following stages:

- (i) By absorption of light energy  $\text{Cl}_2 \rightarrow 2\text{Cl}$ ;
- (ii)  $\text{CO} + \text{Cl} \rightarrow \text{COCl}$ ;
- (iii)  $\text{COCl} + \text{Cl}_2 \rightarrow \text{COCl}_2 + \text{Cl}$ .

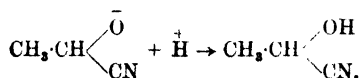
In most cases the reaction appears to be of the ionic type, and to occur at a semipolar bond  $\text{CH}_2 = \text{CH}_2 \rightarrow \overset{+}{\text{CH}}_2 - \overset{-}{\text{CH}}_2$  promoted by the reagent used. In many cases, although the sharing of the electrons is not equal, the link has not reached the state of a complete polar link, the two atoms between the link are polar, one + and the other -, due to the unequal sharing, and can be denoted  $\overset{\delta+}{\text{C}} = \overset{\delta-}{\text{C}}$ , and in the presence of suitable polar reagents this becomes a true semipolar link, viz.  $\overset{+}{\text{C}} - \overset{-}{\text{C}}$ . The ionic character of such reactions is characteristic of many carbonyl additions,  $\overset{+}{\text{C}} = \overset{-}{\text{O}}$ , the O atom always accepting the - charge and hence readily reacting with cations, e.g.  $\text{H}^+$ , whereas the carbon is + and reacts only with anions, e.g.  $\text{CN}^-$ , or with reagents which readily yield anions. As the  $\bar{\text{O}}$  is more stable than the  $\bar{\text{C}}$ , e.g.  $\text{OH}^-$ ,  $\text{OEt}^-$ ,  $\text{OPh}^-$  are all stable, it follows that the  $\bar{\text{C}}$  is the primary centre of attack and therefore addition occurs most readily with compounds giving active anions and not with reagents giving active cations and stable inert anions. The halogens, halogen hydracids, and nitrosyl chloride yield stable anions and hence do not readily form additive compounds with carbonyl compounds. The first reaction to be studied in detail from the ionic view, the formation of cyanhydrins (p. 148, *Lapworth*, J. C. S., 1903, 995), showed that the addition of  $\text{HCN}$  does not



occur with the acid itself, but is immediately started by a trace of alkali, i.e. by the formation of  $\bar{\text{CN}}$ . The primary reaction is



and in order to bring the reaction to completion it is necessary to work in a solution of fairly constant  $p_{\text{H}}$  value, such as  $\text{KHCO}_3$  solution, which supplies  $\text{H}$  ions at a practically constant concentration and thus forms the cyanhydrin

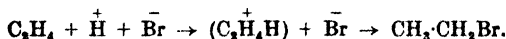


The ionic view of addition is generally accepted for the majority of reactions occurring in solution, both the unsaturated compound and the reagent reacting in the ionic form, often induced by a catalyst, and finally the ions unite to form a covalent compound.

The addition to a double link is a complex reaction, and it is difficult to draw general conclusions as the following factors have an important bearing on the reaction: (1) The polarized state of the unsaturated compound; (2) The influence of temperature, solvent, light and catalysts; (3) The point of attack in an unsymmetrical compound, i.e.  $\alpha$  or  $\beta$ ; (4) Influence of substituents.

Where the two addenda are the same, e.g.  $2\text{H}$ ,  $2\text{Br}$ ,  $2\text{OH}$ , only one compound can be formed, but the rate of formation and the equilibrium (if any) may vary with conditions.

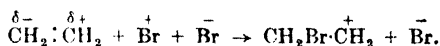
The addition of either bromine or hydrogen bromide to olefines is regarded as an ionic reaction:



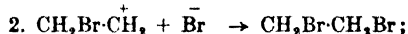
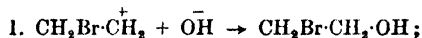
The reaction between ethylene and bromine is a surface reaction (*Steward and Edlund*, 1923), and the glass surface acts as a catalyst. Coating the glass with stearic acid increases the rate of addition, whereas paraffin wax almost completely inhibits it, and this points to the need of a polar catalyst. Water accelerates the reaction and rise of temperature diminishes it, indicating that the reaction is not a mere addi-

tion, but probably depends on the formation of an intermediate product which is less stable at high temperatures. The effect of moisture is also to transform the reaction from one of the 2nd order to one of the 1st, and independent of the bromine concentration, and the intermediate product is probably a hydrated bromine molecule formed so readily on the glass surface that its concentration is practically independent of the bromine concentration in the gas phase (*G. Williams*, 1923). It is the  $+$  ion or positive pole of this hydrate which is reactive.

With aqueous solutions of chlorine (or bromine) chlorhydrins (bromhydrins) are also formed, and to account for all the phenomena *Francis* (1925) has suggested that the first reaction is the addition of  $\text{Br}^+$  derived from the ionized bromine ( $\text{Br}^+$  and  $\text{Br}^-$ ):



The  $\text{CH}_2\text{Br}-\text{CH}_2^+$  ion can then react with the  $\text{Br}^-$  or with the  $\text{OH}^-$  ion derived from the water; as the  $\text{Br}^-$  ion is more stable than the  $\text{OH}^-$  and less liable to lose its ionic charge, it follows that reaction 1 takes place more readily than reaction 2.



i.e. there is a greater tendency for the formation of the bromhydrin than the dibromide. This is confirmed by *Terry* and *Eichelberger's* observation (1925) that the addition of bromide ions (e.g. sodium bromide) increases the yield of dibromide at the expense of the bromhydrin, and the addition of chloride ions gives a certain amount of  $\text{CH}_2\text{Br}-\text{CH}_2\text{Cl}$ .

In non-aqueous solvents the rate of addition of bromine to unsaturated acids of the type of cinnamic acid is extremely slow at the beginning but increases with time owing to the formation of small amounts of hydrogen bromide which acts as a catalyst, and if a definite concentration of hydrogen bromide is used the reaction becomes typically bimolecular and roughly proportional to the concentration of the hydrogen

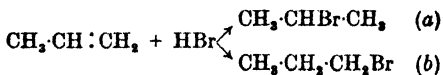
bromide (*Williams and James*, J. C. S., 1928, 343; cf. *Robertson and others*, 1937, 335, and also 1939, 224).

ICl behaves as a catalyst in much the same manner as HBr, and it appears that the catalysts are compounds which can form higher complexes with bromine.

Although most olefine derivatives combine with bromine, compounds in which there are several negative groups, such as Ph, Br, CN, CO<sub>2</sub>H, already attached to the two carbon atoms, do not form additive compounds with bromine (*Hugo and Bauer*, B., 1904, 3317; *H. Ley*, B., 1917, 243), although they contain an olefine linking. They combine, however, with chlorine (*Behr*, B., 1910, 2940; *Meisenheimer*, A., 1927, 456, 142). On the other hand, olefine compounds, containing two methyl groups attached to one of the two ethylene carbon atoms do not readily combine with hydrogen, but form additive compounds with bromine, e.g. dimethyl-styrene, CHPh: CMe<sub>2</sub>, or terpinolene (Chap. LVII, B1).

**Addition of Hydrogen Halides.**—As already pointed out addition occurs most readily with HI and least readily with HCl. Union with HF can also occur (*Grosse and Linn*, J. Org., 1938, 26, cf. J. A. C. S., 1935, 1616), but pressure is required. The reaction is non-catalytic, yields of 80 per cent of additive product can be obtained in certain cases and by-products are polymerized olefines. *Markownikoff* (1870) from known data drew the generalizations: (1) If an unsymmetrical hydrocarbon combines with hydrogen halide the halogen adds to the carbon atom with fewer hydrogen atoms attached to it. (2) By addition of hydrogen halides to vinyl chloride or chlorinated propylene the halogen always adds to the carbon atom which already has halogen attached to it.

Reaction (a) is the normal and (b) the abnormal in generalization (1).



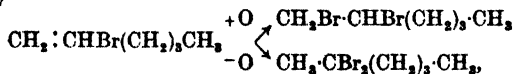
Numerous exceptions to the first generalization are known and are due to the fact that the reaction (b) is favoured by traces of oxygen or peroxides (*Kharasch and others*, J. A. C. S., 1933-37; *Smith and others*, J. C. S., 1934-37, and *Urushibara and Takebayashi*, Ber. C. S. Jap., 1936-37).<sup>\*</sup> In some

<sup>\*</sup> For summary see J. C. Smith, C. and I., 1937, 833; 1938, 461.

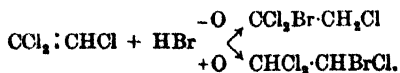
cases the effects of traces of oxygen are so marked on the hydrogen bromide addition that in order to obtain the normal reaction it is necessary to work in the presence of an anti-oxidant, e.g. quinol, diphenylamine, &c., and even the compound being studied or the solvent, e.g. acetic acid, can act as an anti-oxidant.

Some of the generalizations drawn are: (1) That with a terminal double bond HCl adds on very slowly and in the normal manner, and is catalysed by the presence of ferric chloride. (2) That with HBr the reaction is more rapid, is catalysed by ferric chloride, and can be either normal or abnormal according to the absence or presence of oxygen or peroxides. Increase in temperature favours the abnormal reaction and light of all wave-lengths accelerates both reactions. This rule 2 holds good not only for hydrocarbons,  $\text{CH}_2:\text{CH}(\text{CH}_2)_n\cdot\text{CH}_3$ , where  $n = 6, 8, 10, 12, 14$ , or 16, but for acids of the series  $\text{CH}_2:\text{CH}(\text{CH}_2)_n\cdot\text{CO}_2\text{H}$ , where  $n$  varies from 1-8. An exception is acrylic acid ( $n = 0$ ), where the product formed is  $\beta$ -bromopropionic acid under all conditions. The rule also holds for the series  $\text{CH}_2:\text{CH}(\text{CH}_2)_n\text{C}_6\text{H}_5$ , where  $n = 1, 2$  or 4. A few exceptions to the rule relating to oxygen effect are: (a) Undecenol,  $\text{CH}_2:\text{CH}(\text{CH}_2)_8\cdot\text{CH}_2\cdot\text{OH}$ , where apparently the  $\cdot\text{CH}_2\cdot\text{OH}$  group acts as an anti-oxidant, as the acetyl derivative behaves in the usual manner in the presence of peroxides. (b) Styrene,  $\text{CH}_2:\text{CHPh}$ , which gives  $\text{CH}_3\cdot\text{CHBrPh}$  under all conditions. (c) Safrole, eugenol and isoeugenol methyl ether (Chap. XXIV), all of which give the normal product even in the presence of oxidants, although the corresponding unsubstituted compound, allylbenzene, gives the abnormal product in the presence of peroxides.

Exceptions to *Markownikoff's* second rule (p. 824) are met with in the presence of oxidants, e.g. 1-bromo- $\Delta'$ -hexene,  $\text{CHBr}:\text{CH}(\text{CH}_2)_3\cdot\text{CH}_3$  gives  $\text{CH}_2\text{Br}\cdot\text{CHBr}(\text{CH}_2)_3\cdot\text{CH}_3$  in the presence of a peroxide and  $\text{CHBr}_2(\text{CH}_2)_4\cdot\text{CH}_3$  in its absence. Similarly



and also vinyl and allyl bromides, and trichlorethylene,



(3) The addition of HI is rapid, takes the normal course, and is unaffected by oxygen.

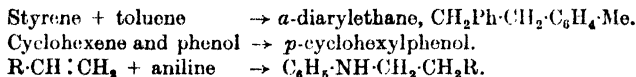
*With a Non-terminal Olefine Bond.*—With a compound containing a non-terminal double bond, e.g.  $\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\text{X}$ , both normal and abnormal additions of HBr occur and often to an equal extent in the case of a hydrocarbon. The reaction is unaffected by oxygen or peroxides, thus  $\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\text{Br}$  gives 80 per cent of  $\text{CH}_3\cdot\text{CHBr}\cdot\text{CH}_2\cdot\text{CH}_2\text{Br}$  and 20 per cent of  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CHBr}\cdot\text{CH}_2\text{Br}$ . When a highly polar group is in close proximity to the double bond, e.g. crotonic acid,  $\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ , the product under all conditions is the  $\beta$ -bromo-derivative, and similarly with vinyl bromide and allyl bromide.  $\Delta^2$ -Pentenoic acid adds on HCl more readily than the  $\Delta^1$ -isomer, and addition is facilitated by using aqueous solutions of HCl, and the reaction is not catalysed by  $\text{FeCl}_3$ .

The effects of oxygen are largely influenced by the solvent, e.g. alcohol and ether appear to act as anti-oxidants, and in the presence of aliphatic acids a large amount of oxygen or peroxide is needed before their effect is obvious. Other substances, e.g. traces of moisture, nitric oxide and ferromagnetic metals, can also act as catalysts for the abnormal reaction (cf. *Smith*, loc. cit., p. 466).

**Other Addenda.**—Olefines form additive compounds with  $\text{NOCl}$ ,  $\text{N}_2\text{O}_3$  and  $\text{N}_2\text{O}_4$ , the addenda being NO and Cl, NO and  $\text{NO}_2$ ,  $\text{NO}_2$  and  $\text{NO}_2$  respectively. These products are of great value in characterizing terpenes (Chap. LVII), and the compounds with  $\text{NOCl}$  readily react with arylamines (primary and secondary), the Cl group being replaced by  $\cdot\text{NHR}$  or  $\cdot\text{NR}_2$ , and the characteristic nitrolamines with definite melting-points are formed.

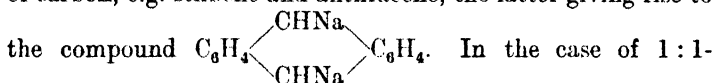
Mercaptans  $\text{HSR}$ , thiocyanogen  $(\text{CNS})_2$  and more complex sulphur compounds, e.g. thioglycollic acid,  $\text{HS}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ , also form additive compounds with olefines, the addenda being H and SR (where R is an alkyl group)  $2\text{CNS}$  or H and  $\text{S}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ . In the latter case, the reaction is catalysed by oxidants and gives the abnormal product, e.g. styrene,  $\text{CHPh}:\text{CH}_2$ , and  $\text{HSR}$  give  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{SR})\cdot\text{CH}_3$ ; in the entire absence of oxygen the reaction is extremely slow, and the normal product,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{SR}$ , is formed (C. and I., 1938, 752).

Aromatic hydrocarbons, phenols and amines can also form additive compounds with olefines:



**Alkali Metals.**—In ethereal solution many compounds containing the groupings C:C, C:N, N:N combine with sodium (*Schlenk* and others, B., 1914, 473), and the structure of the additive compound is deduced from a study of the products formed by the action of water or carbon dioxide. Thus the sodium derivative of stilbene,  $\text{CHPh}:\text{CHPh}$ , yields *s*-diphenylethane with water and *s*-diphenylsuccinic acid with carbon dioxide. In a similar manner the acid,  $\text{CO}_2\text{H}\cdot\text{NPh}\cdot\text{NPh}\cdot\text{CO}_2\text{H}$ , can be prepared from azobenzene.

This additive reaction is by no means general for unsaturated compounds. With olefine compounds only those react with sodium which contain benzene nuclei attached to both atoms of carbon, e.g. stilbene and anthracene, the latter giving rise to

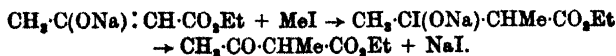


diphenylethylene,  $\text{CPh}_2:\text{CH}_2$ , only the  $\text{CPh}_2$  takes up Na, so that the product is  $\text{Na}\cdot\text{CPh}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CPh}_2\cdot\text{Na}$ . With the C:N linking, addition to both atoms occurs when two benzene nuclei are attached to the C atom, e.g. benzophenoneanil,  $\text{CPh}_2:\text{NPh}$ , yields  $\text{Na}\cdot\text{CPh}_2\cdot\text{NPh}\cdot\text{Na}$ , whereas benzaldehydeanil  $\text{CHPh}:\text{NPh}$  yields  $\text{Na}\cdot\text{NPh}\cdot\text{CHPh}\cdot\text{CHPh}\cdot\text{NPh}\cdot\text{Na}$ .

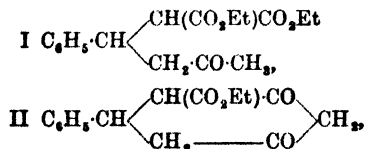
Compounds with sodium attached to two adjacent atoms behave abnormally, with alkyl halides they yield the original unsaturated compound, and a dialkyl, e.g.  $\text{CH}_3\cdot\text{CH}_3$  or  $\text{C}_2\text{H}_5\cdot\text{C}_2\text{H}_5$ ; but when the sodium atoms are in positions 1:4 the reaction is normal and the sodium atoms become replaced by alkyl groups.

Ethyl diazoacetate also combines with certain olefines (cf. Chap. LVII, C1) and results in the elimination of nitrogen and the formation of an ester derived from cyclopropane.

It is highly probable that the reaction between alkyl halides or acyl chlorides and the sodium derivative of ethyl acetoacetate is of an additive character (pp. 258–259) (*Michael*, J. pr., 1899, 60, 295; *Nef*, A., 1899, 266, 52; 1893, 276, 235; 1894, 280, 314).



**Michael Reaction.**—The additive condensation of  $\alpha\beta$ -unsaturated acids, their esters or  $\alpha\beta$ -unsaturated ketones with the sodium derivative of ethyl malonate, ethylacetoacetate, or ethyl cyanoacetate is known as the *Michael* condensation and is of great value for synthesizing numerous compounds. The unsaturated compound should contain a basylous group attached to one ethenoid C atom, and a strongly acylous group, e.g.  $\text{CO}_2\text{H}$ ,  $\text{CO}$ ,  $\text{CN}$ , to the other. Then the sodium always adds on to the latter carbon atom, and the  $\text{CH}(\text{CO}_2\text{Et})_2$  or  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}(\text{CO}_2\text{Et})$  to the former. The esters of fumaric, maleic, aconitic, crotonic, citraconic, itaconic, acetylenedicarboxylic, and phenylpropionic acids and benzylideneacetone, all react in a similar manner but at different rates (*Auwers*, B., 1895, 1131; A., 1896, 292, 147). The presence of  $\text{CO}$  or  $\text{CN}$  attached to one of the olefine C atoms increases the reactivity of the olefine with the above-mentioned esters, and also towards  $\text{HCN}$ , ammonia, amines, hydroxylamine and phenylhydrazine (anionoid reagents), whereas they depress the reaction of olefines with halogens and halogen hydracids (cationoid reagents). The *Michael* reaction is of considerable value for synthesizing polybasic acids, e.g. 2-phenylpropane-1:1:3-tricarboxylic acid can be obtained from ethyl cinnamate and ethyl sodiomalonate, and from benzylidene-acetone and ethyl sodiomalonate the additive compound I,



which readily loses alcohol, giving ethyl phenyldihydroresorci-late II. A modification of the reaction consists of using the free malonic, aceto-acetic, or cyano-acetic ester in the presence of a little diethylamine (*Knoevenagel*, B., 1904, 4464). The sodium salts of the unsaturated acids can sometimes be used instead of the esters (*Reinicke*, A., 1905, 341, 80).

For addition of ethyl malonate to alkyl substituted buta-diene- $\alpha$ -carboxylic ester cf. *Farmer* and *Mehra* (J. C. S., 1930, 1610; 1931, 1904, 2561).

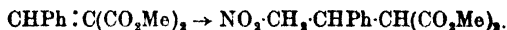
The *Michael* reaction is a balanced one, so that as a rule

yields are not quantitative, but can be improved by removing the condensation product and continuing the reaction.

Hydrogen cyanide, sodium bisulphite, and other compounds can react with olefine compound containing a C:O or C:N group in conjugation with the C:C, i.e.  $\alpha\beta$ -unsaturated acids, their esters, and  $\alpha\beta$ -unsaturated nitriles or ketones, e.g. benzylidene-malonic ester,  $C_6H_5 \cdot CH : C(CO_2Et)_2$  and HCN give  $C_6H_5 \cdot CH(CN) \cdot CH(CO_2Et)_2$  (*Lapworth*, J. C. S., 1903, 995; 1904, 1206; 1906, 945). The reaction is of importance as affording a convenient method of preparing substituted succinic acids.

The reaction of the  $\alpha\beta$ -unsaturated compounds with ammonia, amines, hydroxylamine and phenylhydrazine is of value for obtaining the amide or salt of a  $\beta$ -amino-acid, e.g. crotonic acid,  $CH_3 \cdot CH : CH \cdot CO_2H$ , with aqueous ammonia gives the ammonium salt of  $\beta$ -amino-*n*-butyric acid.

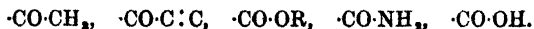
Nitromethane combines with olefine compounds. With unsaturated esters addition takes place in dry methyl alcohol containing sodium methoxide. H adds on to the C atom to which the  $CO_2Et$  group is attached, and  $\cdot CH_2 \cdot NO_2$  to the adjacent C atom; thus the methyl ester of benzylidene-malonic acid:



With an unsaturated ketone, e.g. phenyl styryl ketone, the product is phenyl  $\beta$ -phenyl- $\gamma$ -nitro-ethyl ketone (*Kohler*, J. A. C. S., 1916, 889; 1919, 764):



Addition of hydrogen, hydrogen cyanide, alcohol, sodium bisulphite, *Grignard* reagents, &c., to the carbonyl has already been discussed under aldehydes and ketones (Chap.V). Different carbonyl compounds react at very different rates, and the following is the order of relative reactivity:



Compare also *Goldschmidt*, B., 1896, 105.

In the case of a series of ketones the introduction of acylous groups, e.g.  $CO_2Et$ , increases the reactivity of a ketone, whereas alkyl groups lessen the reactivity of the CO group towards sodium bisulphite (*Stewart*, J. C. S., 1905, 186; *Petrenko*-



*Kritschenko*, A., 1905, **341**, 150). For additions to  $\alpha : \beta$  unsaturated ketones cf. *Vorländer*, *ibid.* p. 9.

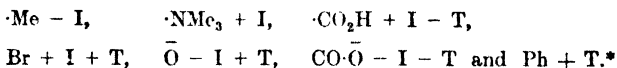
For action of metals on olefines cf. C. and I., 1937, 321.

The relationship between the addition to olefines and tautomeric phenomena and the influence of inductive and tautomeric (electromeric) effects of various substituents has been indicated by *Ingold* and *Ingold* (J. C. S., 1931, 254, 2742, 2746). As already pointed out (Chap. XXXV) the tauto-

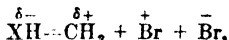
meric effect produced on an unsaturated compound  $>C \rightleftharpoons C<$

is to produce a shifting of electrons so that the difference in density of the electrons produces a small + charge on one and

a corresponding - charge on the other atom,  $>\overset{\delta+}{C} \cdots \overset{\delta-}{C}<$ , which if complete can be represented as  $>\overset{+}{C} - \overset{-}{C}<$ . The effect of any substituent X, e.g.  $XHC=CH_2$ , will be to minimize or increase the difference in electron densities on the two carbon atoms, and the effects of some common substituents are:



As the addition of bromine in solvents is an ionized reaction,



the less stable  $\overset{+}{Br}$  is the more reactive, and hence starts by combining with the C with the slight negative charge, and is finally completed by the more stable  $\bar{Br}$  combining with the other C atom. When X represents a methyl group this tends to repel electrons and hence increase the - charge on the adjacent C atom and the + charge on the other, and will therefore facilitate the addition of  $\overset{+}{Br}$ .

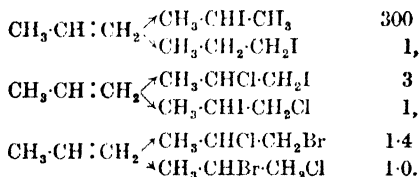
With a  $\cdot CO\bar{O}$  group, e.g. an acid in aqueous solution (e.g. as its sodium salt), both I and T effects are electron repulsing and therefore bromine addition is facilitated.

A bromine atom as substituent has electron-attracting I and T effects, and will have the opposite result and tend to hinder bromine addition.

\* For + and - signs of I cf. Chap. XXXV.

In the addition of HBr and BrCl to cinnamic and phenylpropionic acids (*James and Hanson, J. C. S., 1928, 1935, 2979*), the positive end of the addendum molecule (H in HBr and Br in BrCl) combines with the  $\beta$ -carbon and not with the carbon atom to which the carboxyl group is directly attached.

According to *Michael*, the addition of HI, ICl and BrCl to propene gives the following relative amounts of products:



As the difference in polarity diminishes the ratio of the two possible products falls rapidly.

The addition of HClO, i.e. OH and Cl, to the isomeric hexenoic acids is interesting:

$\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$  gives 100 per cent  $\alpha$ -chloro.

$\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  gives 80 per cent  $\beta$ -chloro and 20 per cent  $\gamma$ -chloro.

$\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  gives 5 per cent  $\gamma$ -chloro and 95 per cent  $\delta$ -chloro-acid.

The addition of HOBr, i.e. Br and OH, to an acid often takes place readily by using bromine water and the potassium salt of the acid. The possible addenda are  $\overset{+}{\text{Br}}$ ,  $\overset{-}{\text{Br}}$ ,  $\overset{+}{\text{H}}$ ,  $\overset{-}{\text{OH}}$ . The  $\overset{+}{\text{Br}}$ , being the less stable cation, adds on to the  $\overset{\delta-}{\text{C}}$  and then the less stable anion, viz.  $\overset{-}{\text{OH}}$  and not  $\overset{\delta+}{\text{Br}}$  to the  $\overset{\delta+}{\text{C}}$  atom. When alcohol is present the addenda are  $\overset{+}{\text{Br}}$  and  $\overset{-}{\text{OEt}}$  as this is less stable than  $\overset{-}{\text{OH}}$ .

In the addition of  $\text{NH}_3$ ,  $\text{NH}_2\text{Me}$  and  $\text{NHEt}_2$  to ethyl crotonate the  $\beta$ -amino- or substituted  $\beta$ -amino-butyrate are always formed:



and by the addition of water to substituted acetylenes, e.g.  $\text{RC}:\text{C}\cdot\text{CH}_2\text{OH}$ , under the influence of mercurous acetate solution

the only products formed are  $R \cdot CO \cdot CH_2 \cdot CH_2 \cdot OH$  or the dehydrated compounds  $R \cdot CO \cdot CH : CH_2$ .

For addition of diazomethane to olefine and acetylene acids cf. pyrazoline compounds (Chap. XLII).

In all double bonds, whether  $C : C$ ,  $C : O$ ,  $C : N$ , &c., the tendency is for the atom with the larger nuclear charge to become negative. Thus in acetone  $(CH_3)_2\overset{\delta+}{C}:\overset{\delta-}{O}$  in its ketone form there is a strong dipole moment  $(CH_3)_2\overset{\delta+}{C}:\overset{\delta-}{O}$  (viz. 2.7), and under the influence of ionic reagents this is activated into a semipolar bond with a full negative charge on the O atom  $(CH_3)_2\overset{+}{C}-\overset{-}{O}$ . It follows that in all additions to carbonyl the proton adds on to the negative oxygen and the residue of the addendum to the carbon. With the  $C : N$  and  $N : O$  double links the uneven sharing of electrons is such as to give polarities of the types  $\overset{\delta-}{N}=\overset{\delta+}{C}<$  and  $\overset{\delta+}{N}=\overset{\delta-}{O}$ , and on complete ionization  $\overset{-}{N}-\overset{+}{C}<$  and  $\overset{+}{N}-\overset{-}{O}$ .

Solvents and sunlight play an important part in many additive reactions. In the case of the isomeric methoxycinnamic acids, the *o*- and *p*-compounds combine with bromine in the dark much more readily than cinnamic acid itself in solution, whereas the *m*-compound under similar conditions is brominated in the nucleus, yielding the 6-bromo-3-methoxy acid, and in order to obtain an addition product it is necessary to work in ultra-violet light and in non-polar solvents (*Jones and James*, J. C. S., 1935, 1600). In the case of the *o*- and *p*-compounds the strong tautomeric effect (+T) of the methoxy group can act via the ring double bonds to the open-chain double bond, whereas in the *m*-compound there is no available mechanism for the transmission of the +T effect from the nucleus to the side chain.

**Colour Test for Unsaturation.**—Tetranitromethane (p. 107) has been used as a reagent for testing for unsaturation. All olefine compounds, with the exception of a few unsaturated acids, give a yellow coloration with the reagent, as do most aromatic compounds with the exception of nitro-derivatives. Substances containing bivalent sulphur or trivalent nitrogen also give colorations, and generally there appears to be a relationship between the amount of residual affinity and the depth of colour—a conclusion which has been confirmed by a study of the absorption spectra of tetranitromethane

with various heterocyclic compounds containing O, S, or N in the nucleus.

The reaction is so delicate, however, that it is often of little practical value as a trace of an unsaturated compound in a saturated compound will give the reaction.

### Properties of Unsaturated Acids as affected by the position of the Double Bond

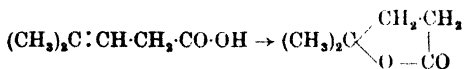
Acids which contain a double bond in the  $\alpha\beta$ -position differ in many respects from isomeric acids in which this bond is further removed from the carboxylic group.

The  $\alpha\beta$ -unsaturated acids are reduced much more readily than their isomerides by sodium amalgam and water, due to the conjugation of C:C with C:O (cf. this Chap., C2). The  $\alpha\beta$ -acids on the other hand combine with bromine much less readily than their isomers (*Sudborough and Thomas*, J. C. S., 1910, 715, 2450; *Williams and James*, 1928, 343; *Ponzio and Gastaldi*, G., 1912, **42**, ii, 92). The rate of addition of bromine to a cinnamic acid is greatly increased by the presence of an *ortho* or *para* methoxy group, and probably by *ortho* or *para* NR<sub>2</sub> groups (J. C. S., 1928, 344; J. I. I. S., 1925, 193). Certain conjugate compounds with one olefine linking in the  $\alpha\beta$ -position to the carboxylic group, e.g. cinnamylidene-acetic acid, combine with bromine fairly readily. The composition of a mixture of  $\alpha\beta$ - and  $\beta\gamma$ -isomeric acids has been determined by *Linstead* (J. C. S., 1927, 356) by comparing the velocity of addition of the mixture with the velocities of the two pure acids.

*J. Bougault* (C. R., 1905, i, 9; cf. *Linstead and May*, J. C. S., 1927, 2566) shows that  $\beta\gamma$ -unsaturated acids combine with the elements of hypiodous acid (HIO), yielding lactones, whereas the isomeric  $\alpha\beta$ -acids do not. This provides the basis of a method for separating a mixture of an  $\alpha\beta$ - and  $\beta\gamma$ -unsaturated acid.

One of the best methods of separating a mixture of  $\alpha\beta$ - and  $\beta\gamma$ -unsaturated acids is due to *Fittig* (B., 1894, **27**, 2667; A., 1894, **283**, 51), and consists in heating the acids for a few minutes at 140° with a mixture of equal volumes of concentrated sulphuric acid and water. The  $\alpha\beta$ -acid is unaffected by this treatment, whereas the  $\beta\gamma$ -acid is converted into a

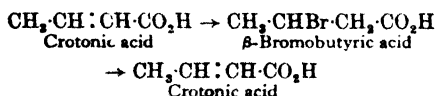
$\gamma$ -lactone (p. 249) which is insoluble in sodium carbonate solution.



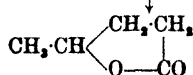
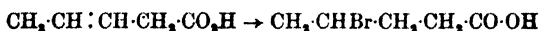
When this method is used, only the  $\alpha\beta$ -acid can be recovered. A method by means of which both acids can be recovered is the separation by fractional esterification, as an  $\alpha\beta$ -acid is esterified much less readily than isomeric unsaturated acids (*Sudborough and Thomas*, J. C. S., 1911, 2307; *Eccott and Linstead*, 1929, 2153).

A method of determining the position of the double bond is by oxidation or by ozonolysis (Chap. XLVIII, G.) as the C:C link is the point of weakness.

Another method adopted for determining the position of an olefine bond is by an examination of the hydrobromide. If the bond is in the  $\alpha\beta$ -position the bromo-derivative of the saturated acid loses hydrogen bromide when treated with alkali and yields the original olefine acid.



A  $\beta\gamma$ - or  $\gamma\delta$ -unsaturated acid also yields a hydrobromide, but when this is treated with alkalis hydrogen bromide is eliminated and a lactone formed.

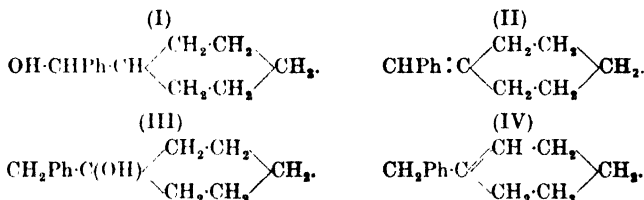


The presence of olefine linkings, as in maleic anhydride, increases to an appreciable extent the readiness with which the anhydride combines with water (*Ribett and Sidgwick*, J. C. S., 1910, 1677).

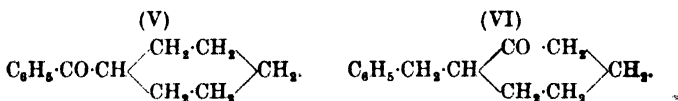
An extremely simple method of determining whether the double bond is in the  $\alpha\beta$ -position or not is by an examination of the rate of esterification of the unsaturated acid and of its saturated analogue by the catalytic method. An  $\alpha\beta$ -acid is esterified much more slowly than its saturated analogue, the  $\beta\gamma$ -isomeride somewhat more readily than the saturated acid,

and acids in which the double bond is still further removed from the carboxyl group have much the same esterification constants as the corresponding saturated acids (*Sudborough and Gittins*).

A method for determining the position of the olefine linking in the case of an unsaturated cyclic hydrocarbon has been worked out by *Auwers and Treppmann* (B., 1915, 1207, 1377). The hydrocarbon formed by the elimination of water from phenylcyclohexyl-carbinol (I) should have the structure represented by (II), but as it is also formed by eliminating water from 1-benzylcyclohexan-1-ol (III) it may have the structure (IV):



By the addition of nitrosyl chloride the Cl attaches itself to the tertiary carbon atom and the NO to the CH group, which becomes transformed into  $\cdot\text{C}:\text{N}\cdot\text{OH}$  group, and this on hydrolysis to CO; the final products would therefore be either benzoylcyclohexane (V) from (II), or 1-benzylcyclohexan-2-one (VI) from (IV):



The actual product isolated was not the known benzoylcyclohexane, and hence was presumably 1-benzyl-cyclohexan-2-one and the original hydrocarbon 1-benzyl- $\Delta^1$ -cyclohexene (II).

For Stereochemistry cf. Chap. X, B., and L, A8.

### C. Polyenes

When several olefine links are present the compounds are termed polyenes, e.g. dienes, trienes, tetrenes, &c., and such compounds may contain both C:C and C:O or C:N groups.

The most interesting and the best-known compounds are those in which the double links alternate with single links, viz. the *conjugated* polyenes. There are, however, many compounds in which the double links are not conjugated; some of the best-known examples are the highly unsaturated acids present as glycerides in vegetable and fish oils (Chap. LV). Such compounds have the properties to be expected from the presence of several double links and react with hydrogen, bromine, &c., in stages. The existence of several olefine links increases the number of possible *cis* and *trans* stereoisomerides.

### 1. DEGREE OF UNSATURATION

It is often necessary to determine the number of olefine links in a given compound. This is accomplished by ascertaining the volume of hydrogen absorbed by a given weight of the substance, and if the mol. wt. of this is known the number of molecules of hydrogen per gram mol. of substance can be calculated and hence the number of olefine links.

This is necessary when the results of analysis render it impossible to distinguish between a formula  $C_{30}H_{56}$  or  $C_{30}H_{54}$ , and also in a polycyclic compound when the number of olefine links will frequently determine the number of rings present (cf. Chap. LXII and LXIV). The method of catalytic hydrogenation (Chap. XLIX, A.) supplies a simple method for determining the number of such links or the **degree of unsaturation**.\* *Fokin* (Abs., 1908, ii, 637) determined the volume of hydrogen absorbed by an alcoholic solution of a given weight of the compound when shaken with molecular platinum. More recently a palladium catalyst on activated charcoal freed from oxygen has been used (B., 1924, 1263); in this case complete reduction occurs at room temperature and pressure in a relatively short time. The method is extremely useful as other double links, C:O, C:N, &c., are not reduced and benzene rings remain intact. *de Kok, Waterman and Westen* (J. S. C. I., 1936, 225T) describe an apparatus which can be used for both volatile and non-volatile compounds. If a platinum catalyst on activated carbon is used benzene rings are also reduced.

The method of determining the **iodine value** in the technical examination of oils and fats (Chap. LV, B.) by ascertaining the

\* For a compound of known molecular weight the number of hydrogen atoms added will not distinguish between two olefine or one acetylene link, but other methods can be used for such differentiation.

amount of  $\text{ICl}$  or  $\text{Br}_2$  added to the oil gives a measure of the degree of unsaturation of the oil in most cases, but is useless for determining the degree of unsaturation when  $\alpha\beta$ -unsaturated acids, or acids with conjugated systems, are present.

## 2. CONJUGATED SYSTEMS

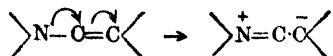
This term was introduced by *Thiele* (1899) for systems containing alternating single and double bonds in the carbon chain, e.g. butadiene,  $\text{CH}_2\text{:CH}\cdot\text{CH}\text{:CH}_2$ , but has since been largely extended and *Robinson* gives the following classification of conjugate systems.

(1) **Polyenoid system.** This is the common type of alternate single and double links between carbon atoms. In a symmetrical butadiene the two double links are equally active, and the 1:2-addition products are the same whichever becomes activated. In an unsymmetrical compound, e.g. 1-phenyl-butadiene,  $\text{CHPh}\cdot\text{CH}\text{:CH}\text{:CH}_2$ , one double bond is more readily activated than the other, and this particular compound gives the 3:4-dibromide,  $\text{CHPh}\cdot\overset{1}{\text{CH}}\text{:}\overset{2}{\text{CH}}\overset{3}{\text{Br}}\text{:}\overset{4}{\text{CH}_2}\text{Br}$ , and in all such cases the product formed depends on the polarity of the substituents and of the addenda.

(2) **Catio-enoid system**, containing an olefine group conjugate with carbonyl or  $\text{C}\text{:N}$ , e.g.  $\text{C}\text{:C}\text{:C}\text{:O}$  or  $\text{C}\text{:C}\text{:C}\text{:N}$ . In these by rearrangement of electrons and links carbon cations are formed:  $\text{>C}=\text{C}=\text{C}=\text{O} \rightarrow \text{>}\overset{+}{\text{C}}-\text{C}=\text{C}-\text{O}^-$  as the O (or N)

forms a more stable anion than cation. The stability of anions is in the order  $\cdot\text{CH}\text{:O} > \cdot\text{CR}\text{:O} > \text{C}\text{:N} > \cdot\text{C}(\text{OEt})\text{:O} > \cdot\text{C}(\text{NH}_2)\text{:O}$ .

(3) **Hetero-enoid system**, containing an olefine link conjugated with a hetero atom, O, S or N, attached by a single link to one of the carbon atoms. The O, S or N hetero atom has a lone pair of electrons which, in the course of addition, can be used to produce a double link between the hetero atom and one of the carbon atoms:

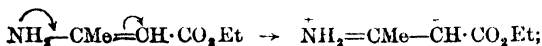


and the extent to which the change occurs depends upon the nature of the hetero atom and also upon the substituents

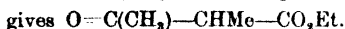
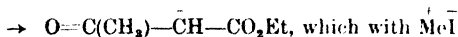
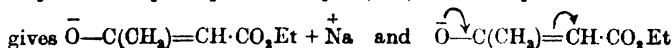
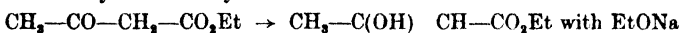


present. The order of mobility of the lone pair of electrons as given by *Kermack and Robinson* (J. C. S., 1922, 433) is  $\bar{\text{N}}\text{H} > \bar{\text{O}} > \text{NH}_2 > \text{OH} > \text{OAc} > \text{I} > \text{Cl}$ , and  $\text{NH}_2 > \text{C}:\text{C}:\text{NH} > \text{CO}:\text{NH} > (\text{CO})_2\text{N}$ , and this is the order of diminishing strengths of bases.

The alkylation of ethyl  $\beta$ -aminocrotonate proceeds as follows:

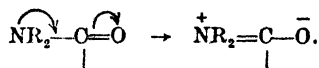


Similarly with ethyl acetoacetate:



(4) **Neutralized system**, containing both an electron donor

and an acceptor, e.g.  $>\text{N}-\overset{|}{\underset{|}{\text{C}}}=\text{O}$  (as in acid amides) or  $-\text{O}-\overset{|}{\underset{|}{\text{C}}}=\text{O}$  (as in carboxylic acids):



A distinct dipole is formed and the carbonyl character is lessened. The formation of the dipole produces association and hence the relatively high boiling-points characteristic of acids. It also offers an explanation of the fact that fatty acids

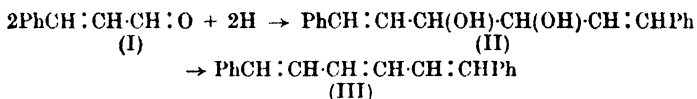
are stronger acids than phenol, e.g.  $\bar{\text{O}}=\text{CR}-\text{OH}$  and  $\text{Ph}-\text{O}-\text{H}$ ,

as the carbonyl group attracts electrons more readily than phenyl. It also accounts for the feebly basic properties of amides as compared with amines, since the formation of the dipole affects both the activity of CO and of  $\text{NR}_2$ .

(5) **Opposed polar systems**, **Dicationoid** and **Dicationoid**, formed by the union of two anionoid groups, e.g.  $\text{NH}_2$ , directly or through C:C groups gives the peroxide system and the  $\alpha$ -diketone and quinonoid systems formed similarly from two

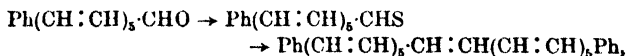
cationoid groups, e.g. CO. Maleic acid is a good example of the latter type,  $\text{OH}\cdot\text{CO}\cdot\text{CH}:\text{CH}\cdot\text{CO}\cdot\text{OH}$ , where the crossed polarities of the two carbonyl groups affect the stability of the C:C bonds and hence tend to produce isomeric change, e.g. conversion of citraconic into itaconic acid under the influence of alkali. (For further detail cf. *Robinson's Lectures*, p. 29.)

**Formation of Conjugated Systems.**—*Kuhn* (J. C. S., 1938, 605) gives a summary of methods used for synthesizing conjugated polyenoid compounds, e.g. 1:6-diphenylhexatriene III is best obtained by reducing cinnamaldehyde I to hydrocinnamoin II, and this with  $\text{P}_2\text{I}_4$  in ethereal suspension gives III:



Another general method is the aldol condensation of an unsaturated aldehyde like cinnamaldehyde with another unsaturated aldehyde, e.g. crotonaldehyde in the presence of piperidine acetate; the product 1-phenyl-undecapentenal  $\text{Ph}(\text{CH}:\text{CH})_5\cdot\text{CHO}$ , readily condenses with benzyl magnesium chloride yielding the alcohol,  $\text{Ph}(\text{CH}:\text{CH})_5\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\text{Ph}$ , and this with  $\text{P}_2\text{I}_4$  yields the polyene  $\text{Ph}(\text{CH}:\text{CH})_6\text{Ph}$ .

A method used for preparing longer chains is the replacement of the O of a polyene aldehyde by S (or Se) by means of  $\text{H}_2\text{S}$  (or  $\text{H}_2\text{Se}$ ) and the removal of the S (or Se) by Cu thus producing a union of two molecules,



1:22-diphenyldodecaundecene, a violet-black solid.

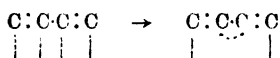
Similar aliphatic aldehydes, e.g.  $\text{CH}_3(\text{CH}:\text{CH})_n\text{CHO}$ , are formed by condensing crotonaldehyde in the presence of piperidine acetate. With  $n = 5$  the product is orange-red, and these aldehydes condense readily with malonic acid in the presence of piperidine yielding the dibasic acids,  $\text{CH}_3(\text{CH}:\text{CH})_n\text{CH}:\text{C}(\text{CO}_2\text{H})_2$ . When  $n = 8$  the product has a deep purple colour.

**Addition to Conjugated Systems.**—*Thiele* drew attention to the fact that in many cases of conjugated dienes addition

occurs terminally, i.e. in the 1 : 4-positions, and not vicinally, i.e. in the 1 : 2- or 3 : 4-positions:



and that the product contains an olefine link in the 2 : 3-position. He introduced the idea of *residual affinities* in connexion with olefine links, and with conjugated systems suggested that the residual affinities of the central carbon atoms are mutually satisfied so that only the residual affinities of the terminal atoms can be used for attracting addenda and he expressed the idea graphically:

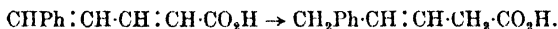


and such residual affinities are equivalent to the incomplete electron migrations denoted by the  $\curvearrowright$  sign of *Ingold*.

Numerous examples of 1 : 4-addition are known:

Butadiene on bromination gives as final product 1 : 4-dibromo- $\Delta^2$ -butene,  $CH_2Br\cdot CH:CH\cdot CH_2Br$ , melting at  $54^\circ$  (C. R., 1893, **116**, 723; **117**, 553), but *Farmer, Lawrence and Thorpe* (J. C. S., 1928, 729) have shown that the first product is a liquid dibromide containing much of the 1 : 2-dibromo- $\Delta^3$ -butene,  $CH_2Br\cdot CH_2Br\cdot CH:CH_2$ , which at  $100^\circ$  passes into an equilibrium mixture containing 20 per cent of the 1 : 2-compound and 80 per cent of the 1 : 4-product.

Cinnamylideneacetic and cinnamylidenemalonic acids on reduction yield 1 : 4-dihydro-derivatives (*Riiber*, B., 1904, 3120):

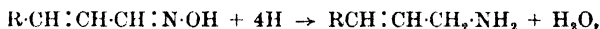


Compounds with conjugate C:C and C:O or two  $\cdot C:O$  links can also form terminal additive compounds, although benzil,  $O:CPh:CPh:O$ , when reduced by ordinary methods yields benzoin,  $O:CPh\cdot CHPh\cdot OH$ , pointing to 1 : 2-addition, yet in the presence of acetic anhydride and sulphuric acid the product is the diacetyl derivative,  $OAc\cdot CPh:CPh\cdot OAc$ , indicating that the primary reduction product is the unsaturated diol,  $OH\cdot CPh:CPh\cdot OH$ , formed by terminal addition of 2H to the benzil molecule, and that the benzoin is formed from this by the change of the enol into the keto form (A., 1899, **306**, 142):



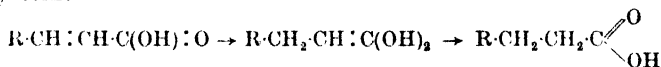
Many conjugated systems give terminal and not vicinal additive compounds with *Grignard* reagents (*Kohler*, Am., 1904-1910).

Terminal addition is not the invariable rule, as shown by the formation of  $\text{CHPhBr}\cdot\text{CHBr}\cdot\text{CH}:\text{C}(\text{CO}_2\text{Me})_2$  from methyl cinnamylidene-malonate and bromine (A., 1904, **336**, 223) and the addition of potassium hydrogen sulphite to cinnamylidenemalononic acid yielding  $\text{CHPh}:\text{CH}\cdot\text{CH}(\text{SO}_3\text{K})\cdot\text{CH}(\text{CO}_2\text{H})_2$  (Am., 1904, **31**, 243), and a similar reaction with HCN. 1:4-Diphenyl-butadiene forms the vicinyl dibromide,  $\text{CHPhBr}\cdot\text{CHBr}\cdot\text{CH}:\text{CHPh}$ ,  $\alpha\beta$ -unsaturated aldoximes and ketoximes yield unsaturated amines (*Harris*, A., 1903, **330**, 193):

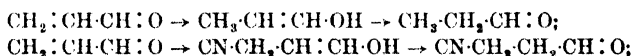


and  $\alpha\beta$ -unsaturated ketones combine with sulphinic acids in the 1:2-position (Am., 1904, **31**, 163).

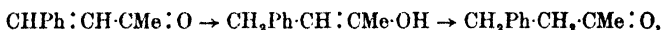
It is well known that  $\alpha\beta$ -unsaturated acids are reduced more readily than their  $\beta\gamma$ -isomers, and this is probably due to the fact that the  $\alpha\beta$ -acids contain a conjugated system and terminal addition occurs, whereas the  $\beta\gamma$ -acids contain no such system:



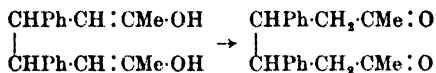
Similarly the addition of hydrogen or hydrogen cyanide to unsaturated aldehydes and ketones is probably a terminal addition followed by rearrangement:



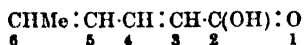
and the reduction of benzylideneacetone,



is primarily a 1:4-addition as the by-product formed is always a  $\beta$ - (not an  $\alpha$ -) pinacone:

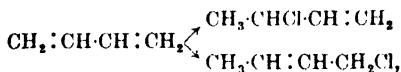


The reduction of sorbic acid (Chap. VI, C.) with 3 conjugated double links has received much attention:

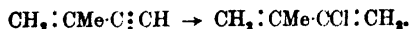


(J. C. S., 1928, 1644, 2343; 1929, 2022; 1932, 430). Both 1:4- and 1:6-addition occur; the former as the result of molecular rearrangement gives  $\Delta^4$ -dihydro-sorbic acid,  $\text{CHMe}:\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OH}$ ,\* and the latter the isomeric  $\Delta^3$ -acid,  $\text{CH}_2\text{Me}\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{COOH}$ . The 1:4-addition is the main reaction, especially in alkaline media. By reduction with a platinum or nickel catalyst at room temperature and pressure the product is mainly  $\Delta^2$ -dihydro, with some  $\Delta^3$ - and  $\Delta^4$ -dihydro acids. With Pt some tetrahydro acid is formed and slight changes in condition, e.g. age of the catalyst, affect the mode of addition.

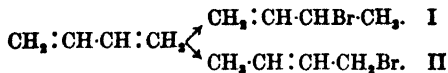
By the addition of hydrogen chloride to a conjugated diene, e.g. butadiene, the hydrogen combines with a terminal C atom (No. 1) and the chlorine with the 2nd or 4th carbon, e.g.:



and similarly when an olefine link is conjugate with an acetylene link; thus vinylacetylene,  $\text{CH}_2:\text{CH}\cdot\text{C}:\text{CH}$ , gives  $\text{CH}_2\text{Cl}\cdot\text{CH}:\text{C}:\text{CH}_2$ , i.e. 1:4-addition, but the product is unstable and yields  $\beta$ -chlorobutadiene,  $\text{CH}_2:\text{CH}\cdot\text{CCl}:\text{CH}_2$ . Isopropenyl-acetylene, isobutenylacetylene and cyclohexenylacetylene all yield 1:2-addition products, e.g.:



Hydrogen bromide in the absence of oxygen and in presence of an anti-oxidant gives a 1:2-additive product; thus with butadiene a 70-90 per cent yield of 3-bromo- $\Delta^1$ -butene I is obtained; whereas in presence of peroxides a 70-90 per cent yield of 1-bromo- $\Delta^2$ -butene II is formed either by direct 1:4-addition or by the rearrangement of the 2-bromo-compound (Karusch and others, C. and I., 1936, 663):



By the addition of HCl at  $-80^\circ$  a 75-80 per cent yield of 3-chloro- $\Delta^1$ -butene is obtained (J. org., 1938, 489).

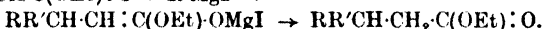
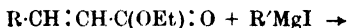
Liquid hydrogen bromide with vinylacetylene gives a 1:4-

\* The C of the  $\text{CO}_2\text{H}$  is termed 1 and the  $\alpha$ -carbon 2.

addition, but as the product is an unstable allene it isomerizes to 2-bromo-butadiene.

Hypochlorous acid reacts with vinylacrylic acid and sorbic acid yielding vicinal additive products, viz.  $\overset{5}{\text{CH}_2}\text{Cl}\cdot\overset{4}{\text{CH}}(\text{OH})\cdot\overset{3}{\text{CH}}:\overset{2}{\text{CH}}\cdot\overset{1}{\text{CO}_2\text{H}}$  and  $\text{CH}_3\cdot\text{CHCl}\cdot\text{CH}(\text{OH})\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ , the  $\Delta^2$ -bond remaining intact and the Cl links up with C No. 5 and OH with C No. 4 (J. C. S., 1932, 2072).

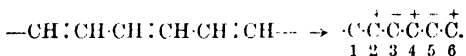
*Grignard* reagents often form 1 : 4-additive compounds with conjugated systems (Kohler, Am., 1904-10; Maxim and Georgesen, Bull. Soc., 1936, [v], 3, 1114). An  $\alpha\beta$ -unsaturated ester and a *Grignard* compound may react so that only the  $\text{-CO}_2\text{Et}$  is involved; the product is then an unsaturated ketone or an unsaturated tertiary alcohol. If, however, the olefine link is also involved and 1 : 4-addition occurs, the final product may be a saturated ester or else the ketone or tertiary alcohol derived from this ester by the further action of the organo-magnesium compound:



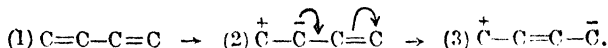
Characteristic of atoms forming a conjugated chain is their alternate positive and negative polarities, as first pointed out by Lapworth (1898), in the case of intramolecular rearrangements, where a mobile group moves from an  $\alpha$ - to a  $\gamma$ -position but never to a  $\beta$ -atom, or, generally, in the movement of a labile group along a chain of alternate single and double bonds the double and single links change places in the path of the labile group. Fuson (Chem. Rev., 1935, 1) draws attention to the fact that the introduction of one or more vinyl groups,  $\cdot\text{CH}:\text{CH}\cdot$ , between  $\text{CH}_3$  and a  $\text{CO}_2\text{Et}$  group does not affect the activity of the  $\text{CH}_3$ . Thus in ethyl acetate and ethyl crotonate the terminal  $\text{CH}_3$  group is active as shown by the condensation with ethyl oxalate. Similarly malonic ester, glutaconic ester and oxalyl-crotonic ester behave similarly with alkylating agents or with diazo-compounds and the terminal  $\text{CH}_3$  groups in all are similar.

It is claimed that most of the phenomena met with in conjugated systems are explicable on the basis of the electronic theory. If the view that the activity of an olefine compound is due to the reagent activating the unsaturated compound so that the double link becomes a semipolar link:

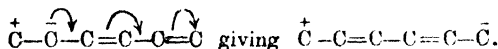
$\cdot\text{CH}:\text{CH}\cdot \rightarrow \cdot\overset{+}{\text{CH}}\cdot\bar{\text{C}}\text{H}\cdot$ , then in a conjugated system there is the possibility of alternate + and - poles:



If a proton adds on to atom No. 1, then the anion of the addendum can add on to atom 2, 4 or 6, but most probably to 6. When the addition has taken place the activity has ceased and the intermediate charges neutralize one another and the system  $\text{CH}\cdot\text{C}:\text{C}:\text{C}:\text{C}\cdot\text{CA}$  is formed with a transposition of double links, as compared with the original. It is highly improbable, however, that the whole molecule becomes activated. *Lapworth* (J. C. S., 1922, 417) regards activity as occurring at one bond only, followed by the migration of one of the ionic charges, thus developed, to an alternate one with the necessary redistribution of covalencies, and this migration is indicated by curved arrows which denote the direction of movement of the ionic charge (tautomeric effect):



A curved arrow is also sometimes used to denote a shift of the double link, in which case it is placed around the carbon atom:



Characteristic of all conjugated systems is their ability to undergo valency rearrangements resulting in the transfer of an electron from one end of the system to the other. This permits of terminal or vicinal addition by the neutralization of the opposite changes of an ionized reagent, and it also permits of the conversion of a 1:2-additive product into the 1:4-product by a process of isomeric changes in which a + or - radical migrates between alternate carbon atoms in the chain.

**Stereo-isomerism.**—Each olefine link in a conjugated system is a potential source of *cis-trans* isomerism; hence with three olefine links conjugated the number of isomerides theoretically possible is large. So far, however, not more than one pair of *cis-trans* isomers has been met with in any such system.

**Stability of a Conjugated System.**—Conjugated systems, as a rule, are more stable than their non-conjugated isomers as shown by their lower heats of combustion, and hence compounds containing two double linkings which are not conjugated frequently undergo molecular rearrangement, under suitable conditions, yielding isomeric products with conjugate linkings. An example is the conversion of limonene into dipentene (Chap. LVII, B1). Another is the existence of moderately stable enolic forms of  $\beta$ -ketonic esters with a conjugated system, whereas  $\alpha$ -ketonic esters do not form enols. Also  $\beta\gamma$ -unsaturated acids isomerize to  $\alpha\beta$ -unsaturated acids under the influence of alkalis (p. 187):



This equilibrium first established by *Fittig* has been examined in detail by *Linstead* and his co-workers, who show that the same equilibrium is attained from either side, but at quite different rates, and that the change is influenced by many factors, including the type of the solvent and the character of the radical R (J. C. S., 1927, 362, 2565, 2579; 1928, 2343; 1929, 1523, 2498). The composition of the equilibrium mixture was ascertained by addition of bromine or iodine (cf. J. C. S., 1927, 2565).

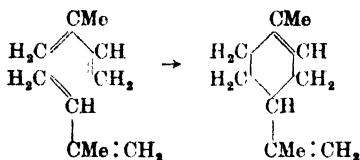
Another example is the conversion of aromatic compounds containing the  $\cdot CH_2\cdot CH:CH_2$  (allyl) into the isomerides containing the  $\cdot CH:CH\cdot CH_3$  (propenyl) group, under the influence of alkali, e.g. allyl-benzene into propenylbenzene, eugenol (p. 483) into isoeugenol, and safrole, the methylene ether corresponding with eugenol, into isosafrole; in this process the C:C of the side chain becomes conjugate with the olefine linkings of the benzene nucleus.

### 3. RING CLOSURE WITH CONJUGATED DIENES

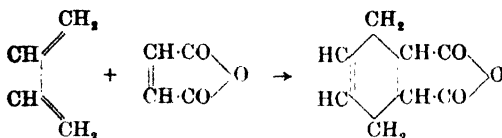
(a) Ring closure as the result of 1:4-addition is frequently observed. The well-known polymerization of isoprene to dipentene (Chap. LVII, A.) is an example. Here the double link in the  $\Delta^1$ -position in one molecule is broken, but the two



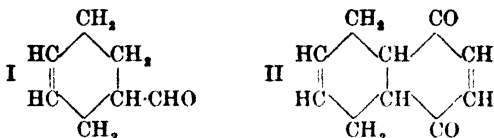
C atoms (still attached by a single link) add on to a second molecule in the 1 : 4-position:



(b) One of the most valuable types of ring closure is that observed when a conjugated system condenses with maleic anhydride (acraldehyde or even benzoquinone). This reaction has value as a method for the diagnosis of such systems, the usual reagent being maleic anhydride, and is also a reaction of considerable synthetic value. The product is invariably a six-membered carbon ring—a partially reduced benzene ring—and the reaction is termed the **Diels-Alder Reaction** (A., 460, 98; 470, 62; 478, 139 (1928-30)).

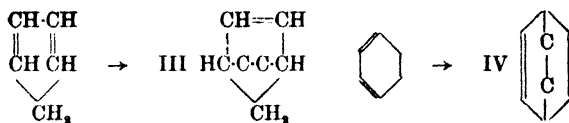


The reaction is the usual 1 : 4-addition to the diene and the formation of a 2 : 3-olefine link in the diene. The compounds formed from butadiene and acraldehyde or benzophenone are represented respectively by formulæ I and II:



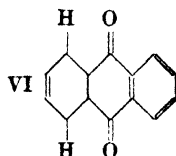
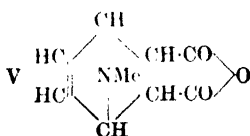
The reaction is also characteristic of cyclic dienes, e.g. *cyclopentadiene* and *cyclohexadiene*, and also heterocyclic dienes, e.g. *furane* and *N-methylpyrrole*. The compounds formed from *cyclopentadiene* and *cyclohexadiene* are given in

III and IV, where the bridge  $\cdot\text{C}\cdot\text{C}\cdot$  denotes the  $\begin{array}{c} -\text{C}\cdot\text{CO} \\ | \\ -\text{C}\cdot\text{CO} \end{array} \text{O}$  group from maleic anhydride.



By this method it is possible to synthesize bridged derivatives with a  $\cdot\text{CH}\cdot\text{CH}\cdot$  in the 1:4-position in cyclohexane.

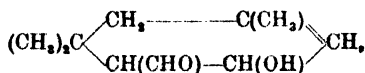
The compound from N-methylpyrrole and maleic anhydride is represented by V, and that from butadiene and  $\alpha$ -naphthoquinone by VI.



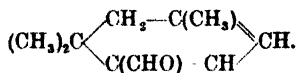
Compounds with two or more conjugated diene systems can unite with two molecules of maleic anhydride, and with compounds of the type  $\text{C}_6\text{H}_5[\text{CH}:\text{CH}]_n\text{C}_6\text{H}_5$  addition always begins at the two ends of the chain.

In the *Diels-Alder* reaction a deep coloration is first noted, but this disappears as the reaction is completed and may be due to the first stage of the addition corresponding with the attachment of the addendum to one end of the conjugated system.

A condensation or polymerization analogous to the *Diels-Alder* reaction is observed when sodamide reacts with an unsaturated aldehyde, e.g. methylcrotonaldehyde,  $(\text{CH}_3)_2\text{C}:\text{CH}\cdot\text{CHO}$ . One molecule reacts as the enol with the conjugate structure,  $\text{CH}_2:\text{C}(\text{CH}_3)\cdot\text{CH}:\text{CH}\cdot\text{OH}$ , and to this the second molecule is added, forming:

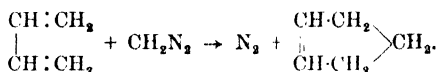


and finally by the loss of water:



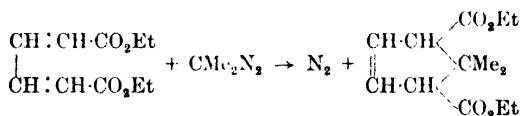
(c) Diazomethane (Chap. IV, F.) and substituted diazomethanes, e.g. ethyl diazoacetate, unite with conjugated di-

olefines eliminating nitrogen and yielding cyclic compounds, e.g. diazomethane and butadiene yield cyclopentene:

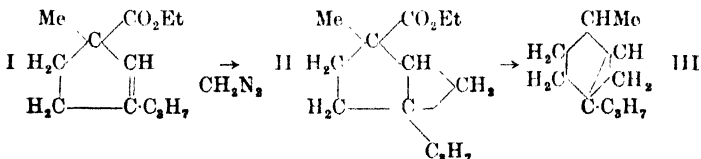


For other examples cf. Chap. IV, F., and LVII, C1.

Aliphatic diazo-compounds also unite with mono-enes. An interesting synthesis of ethyl isodehydrocamphorate is by the action of dimethyl-diazomethane on ethyl muconate (B., 1937, 2109):



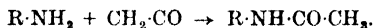
and thujane III has been synthesized from diazomethane and ethyl 1-methyl-3-isopropyl- $\Delta^2$ -cyclopentene-1-carboxylate I by hydrolysing the resulting ester II and eliminating  $\text{CO}_2$ .



## D. Ketens

Wilsmore (J. C. S., 1907, 1938; 1908, 946) has isolated the simplest possible ketone,  $\text{CH}_2:\text{CO}$ , which he terms **keten**, and which may be regarded as a new anhydride of acetic acid. It is obtained by the action of a hot platinum wire on acetic anhydride; numerous other substances are formed at the same time, but a 10 per cent yield can be obtained. Another method is to pass acetone (or isopropyl alcohol) over copper or through molten lead at  $700^\circ\text{--}750^\circ$ ; the yield is 38 per cent of the acetone used together with 46 per cent of methane and 16 per cent of carbonic oxide. It is a colourless gas at the ordinary temperature, has a characteristic odour, and reacts with hydrogen chloride, ammonia, and aniline, yielding acetyl chloride, acetamide, and acetanilide respectively, i.e. it is an

acetylating agent and in many cases is preferable to acetic anhydride as no water is formed:

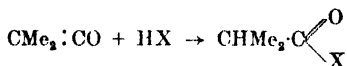


It is usually passed directly into the compound to be acetylated. Aliphatic tertiary alcohols can be acetylated by this method. When kept for some time it polymerizes, yielding **cyclobutane-**

**1 : 3-dione**,  $CH_2 \begin{array}{c} \diagup CO \diagdown \\ \diagdown CO \diagup \end{array} CH_2$ , b.-pt.  $126^\circ$ – $127^\circ$ , which combines

with water to acetoacetic acid (p. 259), and with aniline to acetoacetanilide (J. C. S., 1910, 1978). The dione constitution is not accepted by *Schroeter* (B., 1916, 2697), who points out that true derivatives of the dione differ completely from these polymerization products.

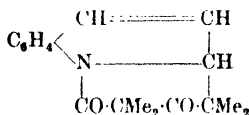
Homologues of keten, e.g. **dimethyl-keten**  $(CH_3)_2C:CO$ , and **diphenyl-keten**,  $(C_6H_5)_2C:CO$  (*Staudinger*, B., 1905, 1735; 1906, 968; 1907, 1145, 1149; *Ott*, A., 1913, **401**, 159), have also been prepared. The method consists in the action of zinc on  $\alpha$ -bromoisobutyryl bromide and diphenyl-chloro-acetyl chloride respectively. The compounds are unstable and readily polymerize. Dimethyl-keten forms stable compounds with tertiary amines, and with water, alcohol, or amines gives isobutyric acid, its ester or amide:



The presence of a keten group,  $\cdot CH_2\cdot CO\cdot$ , is of great importance in the syntheses of numerous cyclic compounds (cf. *Collé*, J. C. S., 1907, 1806).

The homologues are frequently divided into (a) aldoketens, (b) ketoketens. The aldo group comprises keten, its monoalkyl substituted derivatives, and carbon suboxide. They are colourless, incapable of autoxidation, and are polymerized by pyridine. The keto group consists of the dialkylated derivatives. These are coloured, readily undergo autoxidation, and form additive compounds with tertiary amines, such as pyridine, quinoline, and acridine. These products from dialkyl ketens and tertiary amines are stable and have basic properties; they contain two molecules of keten combined with

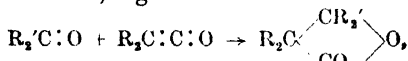
one of the base, and the compound with quinoline is represented as



(A., 1910, **374**, 1). They also form additive compounds with substances containing the groupings C:O, C:N and N:N; for example, *Schiff's* bases and quinones. Diphenyl-keten and quinone yield the  $\beta$ -lactone,  $\text{O} : \text{C}_6\text{H}_4 \begin{array}{c} \text{CPh}_2 \\ \diagup \quad \diagdown \\ \text{O} \end{array} \text{CO}$ , which decom-

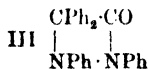
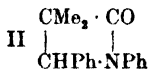
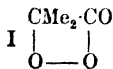
poses into  $\text{CO}_2$  and  $\text{O} : \text{C}_6\text{H}_4 : \text{CPh}_2$ , diphenyl-quinomethane, when heated (*Staudinger*, B., 1908, 905, 1355, 1493).

In the ketens the carbonyl group has not the same reactivity as in ordinary ketones, e.g. it does not form phenylhydrazones or semicarbazones. The ketens also react readily with aldehydes and ketones, i.e.  $\text{R}'\text{HC}:\text{O}$  and  $\text{R}_2'\text{C}:\text{O}$ , the compounds formed are  $\beta$ -lactones, e.g.:



which are extremely unstable and decompose into tetra-alkylated olefines and  $\text{CO}_2$ .

The autoxidation products are probably I, the compounds with *Schiff's* bases II, and with azo-compounds III.



The similarity in structure between an aldoketene  $\text{R} \cdot \text{CH}:\text{C}:\text{O}$  and an alkyl isocyanate  $\text{R} \cdot \text{N}:\text{C}:\text{O}$  corresponds with a certain similarity in chemical properties (*Stewart*).

## E. Unsaturation and Physical Properties

Unsaturation, especially in the case of compounds with conjugate linkings, produces a marked effect on numerous physical properties. The phenomena which have been most closely studied are those on the refraction and dispersion of light. The

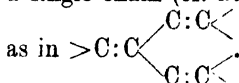
effect of a conjugate linking such as that in  $\text{CHMe}:\text{CH}\cdot\text{CH}:\text{CHMe}$ , is to produce a considerable increase or *exaltation* in the specific and molecular refraction and dispersion. In the case mentioned the molecular refraction is about one unit greater than the value calculated from the atomic refractions + two olefine linkings. The existence of such exaltation is frequently used as an argument in favour of the presence of conjugate linkings (either two olefine or an olefine and carbonyl) in the compound examined. In the case of hexatriene,  $\text{CH}_2:\text{CH}\cdot\text{CH}:\text{CH}\cdot\text{CH}:\text{CH}_2$ , the exaltation is 2.06 units. Exaltation is also observed when an acetylene linking is in conjugation with a carbonyl group. According to *Moureau* (*Annales*, 1906, [8], 7, 436), and *Müller and Bauer* (*J. Chim. phys.*, 1903, 1, 190), the exaltation in certain series of compounds increases with the negative character of the substituents. Little or no exaltation is met with in the case of benzene, furane, diacetyl, and similar compounds, although the formulæ usually written for these compounds contain conjugate bonds. This may be due to special symmetrical ring structure. Hetero atoms with donor electrons such as N in  $\text{NH}_2$ , O in OH, and S in SH when conjugate to double bonds also produce exaltation (*Eisenlöhr*, B., 1911, 3188; *Price and Twiss*, J. C. S., 1912, 1259). Exaltation is extremely well marked in compounds containing conjugate linkings, which, in their turn, are conjugate to the ethylene bonds in phenyl groups: e.g. 1 : 4-diphenyl-butadiene,  $\text{CHPh}:\text{CH}\cdot\text{CH}:\text{CHPh}$ , has an exaltation of 15 units; cinnamylideneacetic acid,  $\text{CHPh}:\text{CH}\cdot\text{CH}:\text{CH}\cdot\text{C}(\text{OH})\cdot\text{O}$ , of 10.5 units, and diphenyl-hexatriene,  $\text{CHPh}:\text{CH}\cdot\text{CH}:\text{CH}\cdot\text{CH}:\text{CHPh}$ , of 24 units (*Smedley*, J. C. S., 1908, 376).

The enormous exaltations which phenyl groups produce on the molecular refractions of compounds like butadiene and hexatriene has been brought forward as an argument in favour of *Kekulé's* formula for benzene, as the three nuclear olefine linkings, which are themselves conjugate, are also conjugate with the olefine linkings in the diene or triene chain. On the other hand, benzene and its simple derivatives show little or no exaltation, and it is possible that the introduction of unsaturated side chains produces a change in the structure of the benzene ring itself.

Some of the most accurate work on unsaturated compounds has been carried out by *Auwers* and *Eisenlöhr* (*J. pr.*, 82, 65; 84, 1, 37; *Auwers* and *Moosbrugger*, A., 1912, 387, 167; *Auwers*

and *Ellinger*, *ibid.* 200, B., 1910, 806; 1911, 3514; 1912, 2764). They compare the specific refractions  $\times 100$ , and not molecular refractions, and make use of the following values for atomic refractions,  $n_D$ , as determined by *Eisenlöh*r (Zeit. phys., **75**, 585);  $\text{CH}_2 = 4.618$ ,  $\text{C} = 2.418$ ,  $\text{H} = 1$ ,  $\text{O}$  (in carbonyl) = 2.211,  $\text{O}$  (in ethers) = 1.643,  $\text{O}$  (in hydroxyl) = 1.525,  $\text{Cl} = 5.967$ ,  $\text{Br} = 8.865$ ,  $\text{I} = 13.900$ , olefine linking = 1.733, and acetylene linking = 2.398. They find that a single conjugation in a hydrocarbon produces an exaltation of approximately 1.9 units, but that this value is reduced to an appreciable extent by the introduction of substituents. The amount of this interference depends upon the number and position of the substituents. In styrene and its  $\beta$ -substituted derivatives the exaltation is about 1.0, and when three substituents are present the exaltation is only 0.45. They conclude that for a given type of compound the exaltation is fairly constant, and within such limits the existence of the exaltation may be made use of in discussions bearing on constitution.

When several pairs of conjugate linkings are present, it is found that the exaltation is much greater when these all form a single chain (cf. hexatriene) than when they are "crossed"



Semicyclic double bonds (p. 962) and rings formed of three atoms, e.g. trimethylene, also produce optical exaltation.

For effects of unsaturation on optical activity see *Frankland* and others, J. C. S., 1906, 1854, 1861; 1911, 2325; *Hilditch*, J. C. S., 1908, 1, 700, 1388, 1618; 1909, 331, 1570, 1578; 1910, 1091; 1911, 218, 224; Zeit. phys., 1911, **77**, 482; *Rupe*, A., **373**, 121.

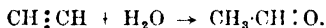
Conjugated systems give absorption bands of a particular type, viz. of greater intensity and lower frequency than those of non-conjugated systems. In hydrocarbons with two or three conjugated bonds the absorption is restricted to the ultra-violet, but with more than four such links the absorption may reach the visible portion of the spectrum, and compounds like bixin (Chap. LXIV, A.) and *p*-quinone are distinctly yellow. The effect of increasing the number of conjugated double links on the intensity of the absorption and in displacing the absorption maximum towards longer wave-lengths is well

illustrated in the series of acids  $\text{CH}_3(\text{CH}:\text{CH})_n\text{CO}_2\text{H}$ , where  $n = 1, 2, 3$  or  $4$  (*Heilbron*, J. S. C. I., 1937, 163T). This generalization has also been of value in the study of the carotenoids (Chap. LXIV, A.), where the relationship between the positions of the absorption bands and the number and character of the conjugated unsaturated centres has proved of great value in confirming the presence of particular chromophores in polyenoid pigments of undetermined constitution.

An aliphatic hydrocarbon must possess 5 or 6 conjugated olefine links in order to be coloured, and as C:O has roughly 1.5 times the value of C:C, the acid decatetrenoic acid is coloured an intense yellow, the acid with 3 C:C and 1 C:O conjugated is colourless (cf. *Allsopp*, P. R. S., 1934, A., **143**, 624). A comparison of camphor (C:O), methylene-camphor (C:O + C:C), benzyl-idenecamphor (C:O + C:C + C:C), and camphor-quinone (C:O + C:O) shows a passage from colourless to blue absorption.

## F. Acetylenes

The acetylenes,  $\text{C}_n\text{H}_{2n-2}$ , are highly unsaturated and, chemically, are extremely reactive, and within the last 20 years acetylene, mainly from calcium carbide, has served as a source from which numerous carbon compounds have been synthesized, many on the commercial scale. The starting-point for many of these syntheses is the formation of acetaldehyde from acetylene:



The usual process is to pass a rapid current of acetylene through 6 per cent sulphuric acid to which mercuric oxide is added and the whole mechanically stirred at a temperature of  $60^\circ$ – $65^\circ$  when a 95 per cent yield on the acetylene used can be obtained. The impure mercury which collects is removed and electrolytically converted back into the oxide.

The acetaldehyde in its turn is used for the manufacture of numerous other products including:

1. **Alcohol** by process of dehydrogenation with copper (Chap. XLIX, C.). The method is not as a rule used in industry.
2. **Acetic acid**.—A 99 per cent pure acid can be obtained by



a single fractional distillation of the oxidation liquor from acetaldehyde. For this purpose the aldehyde, often dissolved in acetic acid, is aerated at a temperature of  $20^{\circ}$ – $25^{\circ}$  in the presence of a little (0.5 per cent) manganese acetate, the temperature rising to  $65^{\circ}$  and the pressure to 75 lb. per sq. in.

3. **Acetic anhydride**, by the catalytic dehydration of the acid using phosphoric acid or sodium metaphosphate at  $150^{\circ}$ – $200^{\circ}$ .

4. **Paraldehyde** (Chap. V, A.).

5. **Ethyl acetate**.—The polymerization of acetaldehyde to ethyl acetate,  $2\text{CH}_3\cdot\text{CHO} \rightarrow \text{CH}_3\cdot\text{CO}\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$ , is readily brought about by small amounts of aluminium alkyl oxides, e.g.  $\text{Al}(\text{OEt})_3$ ,  $\text{Al}(\text{OBu})_3$ . Ethyl acetate can also be obtained from ethyl alcohol with a copper-chromium oxide catalyst at  $220^{\circ}$  and high pressures, the process being one of dehydrogenation followed by polymerization.

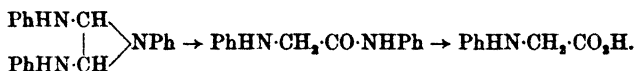
6. ***n*-Butyl alcohol**.—The demand for this alcohol as a solvent is so great that the amount supplied by the fermentation process (Chap. LXIX, B.) is insufficient and it is now also manufactured from acetaldehyde in the following stages: (1) Acetaldehyde  $\rightarrow$  aldol (p. 154). (2) Aldol  $\rightarrow$  crotonaldehyde and water by distillation. (3) Crotonaldehyde  $\rightarrow$  *n*-butaldehyde by catalytic hydrogenation in vapour phase. (4) Butaldehyde  $\rightarrow$  *n*-butyl alcohol by dehydrogenation in vapour phase. This is a fairly general method for preparing alcohols (cf. *Morgan and Hardy*, C. and I., 1933, 518).

7. **Ethylidene diacetate**,  $\text{CH}_3\cdot\text{CH}(\text{OAc})_2$ , is formed together with vinyl acetate,  $\text{CH}_2\text{:CH}\cdot\text{OAc}$ , b.-pt.  $73^{\circ}$ , when acetylene is passed into acetic acid containing 2 per cent  $\text{SO}_3$  and  $\text{HgO}$  at  $50^{\circ}$ – $60^{\circ}$ . The latter distils over with any acetaldehyde formed, whereas the former remains in the vessel. When strongly heated, especially with a small amount of a dehydrating agent, the diacetate decomposes into acetaldehyde and acetic anhydride which are readily separated. The process is used on the large scale for the manufacture of the anhydride.

8. **Polymerization of Acetylene**.—Aromatic hydrocarbons are formed by passing crude acetylene (from methane) over activated charcoal or silica gel at  $600^{\circ}$ – $700^{\circ}$ .

**Cuprene or carbene**—a polymerized acetylene—formed by treating acetylene with copper by silent electric discharge, is a solid, and is used as a substitute for charcoal in the manufacture of explosives.

9. **Chlorinated Products from Acetylene.**—**Tetrachloroethane**,  $\text{CHCl}_2\cdot\text{CHCl}_2$ , is manufactured by passing chlorine and acetylene up a tower filled with quartz and iron borings over which runs a stream of the tetrachloride. It is a heavy liquid, b.-pt.  $147\cdot2^\circ$ , known as **westron**, and is used as a solvent for cellulose acetate. It is toxic, attacks metals in the presence of moisture, and is generally manufactured for the production of other chloro-derivatives, e.g. **trichloro-ethylene**,  $\text{C}_2\text{HCl}_3$ , b.-pt.  $88^\circ$ . This is known as **westrol**, and is formed by heating the tetrachloro-compound with aqueous ammonia in an autoclave at  $140^\circ$ – $170^\circ$ , by passing ammonia through a mixture of the tetrachloride and water at  $60^\circ$ – $70^\circ$ , also by the action of milk of lime or dilute alkalis on the tetrachloride. It can also be obtained from acetylene, chlorine and hydrogen chloride in one operation, care being taken to avoid explosions by using an inert gas and pumice treated with metallic salts as a catalyst. It is quite stable towards dilute acids and alkalis, but hot concentrated alkalis give salts of glycollic acid. It is used in the manufacture of phenylglycine by heating an aqueous suspension with milk of lime (or preferably alkali hydroxides, carbonates, silicates or aluminates) and aniline. The intermediate product is ethylene triphenyltriamine (*Sabanjeff's* base), which hydrolyses to phenylglycine anilide and finally to phenylglycine:



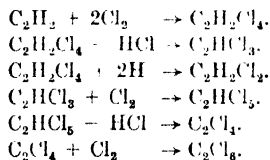
Trichloroethylene and concentrated sulphuric acid yield monochloroacetic acid (Chap. VI, D.), and with chlorine it yields **pentachloroethane**,  $\text{C}_2\text{HCl}_5$ . The trichloro-compound is less toxic than the tetrachloride, is stable in the dark, but is usually mixed with a stabilizer, e.g. hydrocarbon, phenol or alkylamine (1 per cent). It is largely used for the extraction of fats and oils. Its advantages are its low boiling-point, low toxicity, stability, non-corrosive properties, and penetrating power due to its low surface tension and viscosity. It is also used for cleansing metal surfaces, e.g. before plating or galvanizing, as a fumigant for seeds, owing to its germicidal properties and in textile soaps for removing grease in laundry work.

**Dichloroethylene**,  $\text{CHCl}:\text{CHCl}$ , obtained from tetrachloroethane and water vapour in contact with iron, zinc or aluminium, is a mixture of 2 stereoisomerides (b.-pt.  $48.4^\circ$  and  $60.3^\circ$ ).

**Perchloroethylene**,  $\text{C}_2\text{Cl}_4$ , b.-pt.  $120.8^\circ$ , is formed by the action of milk of lime on pentachloroethane. Its chief uses are as a solvent for oil or fat extraction, in textile soap manufacture, and for the treatment of hook-worm and liver fluke in sheep.

**Hexachloroethane**, perchloroethane,  $\text{C}_2\text{Cl}_6$ , a solid, melting and subliming at  $185^\circ$ , is formed by the action of chlorine or perchloroethylene.

The relationships of these chloro-derivatives are shown as follows:



For physical constants cf. Thorpe's Dict., Supp. Vol. I, p. 28.

10. **Ketones from Acetylenes. Acetone from Acetylene.**—A good yield of acetone is formed by passing acetylene at  $350^\circ$ – $450^\circ$  over potassium thorium carbonate on pumice, or a mixture of ferric and manganous oxides or rusty iron shavings at  $500^\circ$ . Acetone is also formed from acetaldehyde and steam over suitable catalysts, e.g. rusty iron and calcium acetate.

Disubstituted acetylenes and water yield ketones, e.g. tolane,  $\text{CPh}:\text{CPh}$ , gives  $\text{COPh}\cdot\text{CH}_2\text{Ph}$ , and phenylpropionic ester gives benzoyl-acetic ester,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ .

11. **Tertiary Alcohols from Acetylenes.**—In the additive reaction between acetylene and a ketone one H of the acetylene becomes attached to the O of the  $\text{C}:\text{O}$  group and the  $\text{C}:\text{CH}$  group to the C of the  $\text{CO}$ . Thus methyl ethyl ketone and

acetylene yield 70 per cent of 
$$\begin{array}{c} \text{Me} \quad \text{OH} \\ \quad \diagdown \quad \diagup \\ \quad \text{C} \\ \quad \diagup \quad \diagdown \\ \text{Et} \quad \text{C}:\text{CH} \end{array}$$
 by adding the

ketone gradually to a suspension of potassium hydroxide in ether saturated at  $-10^\circ$  with acetylene and passing in

more acetylene for 8 hours. By the action of  $\text{MgSO}_4$  at  $230^\circ$  the tertiary alcohol loses water forming the hydrocarbon  $\text{CH}_3\text{:CH:CMe:C:CH}$  with conjugated double-triple links.

**12. Vinyl Compounds from Acetylene** (*Staudinger and Schwalbach, A., 1931, 488, 8*).

Acetylene and hydrogen chloride under pressure give vinyl chloride,  $\text{CH}_2\text{:CHCl}$ , and acetylene and methyl chloride under similar conditions yield propenyl chloride,  $\text{CH}_3\text{:CH:CHCl}$ , isomeric with allyl chloride.

Resinous polymerization products are formed by exposing gaseous vinyl chloride or its solutions in organic solvents to ultra-violet rays or ozone.

Esters such as vinyl acetate,  $\text{CH}_2\text{:CH}\cdot\text{OAc}$ , are formed from acetylene and carboxylic acids under pressure in presence of suitable catalysts, e.g. compounds of Hg, Mg, Sn, Cu, or acetic anhydride.

Vinyl ethers are formed by the action of alcohols under pressure on vinyl-sulphuric acid,  $\text{CH}_2\text{:CH}\cdot\text{O}\cdot\text{SO}_3\cdot\text{OH}$ , which is obtained from acetylene and concentrated sulphuric acid at  $0^\circ$  in the presence of  $\text{HgSO}_4$ , e.g. vinyl-sulphuric acid and ethyl alcohol yield ethyl vinyl ether,  $\text{CH}_2\text{:CH}\cdot\text{OEt}$ , which can also be obtained by passing acetylene under pressure into a mixture of ethyl alcohol and sulphuric acid. Some of these ethers are used for destroying pests.

Vinyl acetate, b.-pt.  $73^\circ$ , is manufactured on a large scale, as it polymerizes under the influence of light and peroxides to valuable resins (cf. *Plastics, Chap. LX*).

**13. Nitrogenous Compounds from Acetylene.**—Acetylene and ammonia over bauxite at  $350^\circ$  yield acetonitrile, and by using oxides of Zn, Th, Zr deposited on silica gel pyridine bases are formed, e.g.  $\alpha$ - and  $\gamma$ -methylpyridines by using  $\text{ZnCl}_2$  and quinoline by replacing the ammonia by aniline.

**14. Sodium Acetylene as a Synthetical Reagent.**—The sodium compound  $\text{NaH:CH}$ , is extremely reactive and can be used for the following synthetical reactions:

(1) With an alkyl iodide to yield alkylated acetylenes  $\text{RC}\equiv\text{CH}$ .

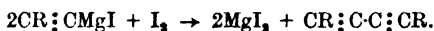
(2) With  $\text{CO}_2$  or  $\text{Cl}\cdot\text{CO}_2\text{Et}$  to give carboxylic acid or ester, e.g. with  $\text{CO}_2$  a 93 per cent yield of propiolic acid is obtained.

(3) With acyl chlorides,  $\text{:R}\cdot\text{COCl}$ , to give unsaturated ketones  $\text{R}\cdot\text{CO}\cdot\text{C:CH}$ .

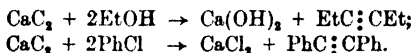
These sodium compounds can be obtained by the action of

sodium on mono-alkylacetylenes or by the action of sodamide on acetylenes (C. R., 1924, 178, 777).

15. **Homologues of Acetylene**,  $RC:CH$  and  $RC:CR'$ .—When strongly heated with alcoholic potash ethyl-acetylene,  $EtC:CH$ , changes to dimethylacetylene,  $MeC:CMe$ ; but the reverse change occurs by heating dimethyl-acetylene with sodium or sodamide; thus methylethylacetylene yields a sodium propyl-acetylene and some 1:1-dimethyl-allene. This formation of substituted allenes is the chief product when the alkyl group is branched, e.g. isopropyl. Conjugated diacetylenes are formed by the action of iodine on acetylenic *Grignard* compounds:



Disubstituted acetylenes are formed by the action of alcohols, phenols, or halogen derivatives on carbides:

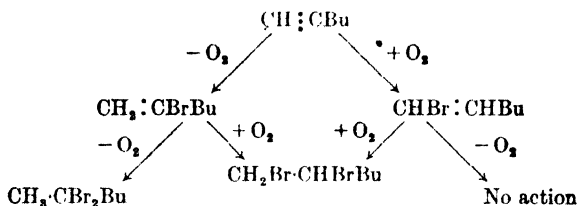


In the addition of halogens to acetylene derivatives the addition is often *trans* but sometimes *cis*. *Ramaswami Ayyar* (J. I. I. S., 1935, 123) gives the following numbers for the relative proportions of *cis* and *trans* dibromides formed from phenylpropionic acid ( $C_6H_5 \cdot CH:CH \cdot CO_2H$ ) in chloroform solution:

		<i>cis</i>	<i>trans</i>
Acid	dark 0° →	3	2
	daylight 0-25° →	2	1
Methyl ester	dark 0° →	1	2
	daylight 0-25° →	1	3

The addition of  $HBr$  to alkylacetylenes is similar to that to olefines (this Chap., B.). In the complete absence of oxygen normal addition takes place, but in the presence of oxygen abnormal addition (*Harris and Smith*, J. C. S., 1935, 1572; *Young, Vogt and Nieuwland*, J. A. C. S., 1936, 1806). The following

scheme illustrates the addition of HBr to *n*-butylacetylene:

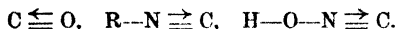


As already pointed out a conjugated double and triple bond behave similarly to a conjugated diene.

## LII. COMPOUNDS WITH ABNORMAL VALENCY: FREE RADICALS

### A. Compounds with Bivalent Carbon

Carbon monoxide, carbylamines, and fulminic acid, viz.  $\text{C} \cdot \text{O}$ ,  $\text{R} \cdot \text{N} \cdot \text{C}$ ,  $\text{H} \cdot \text{O} \cdot \text{N} \cdot \text{C}$ , were usually represented as containing a bivalent C atom. They are now usually represented as having a co-ordinate link between O and C or N and C, the O or N acting as donor to carbon:



In each of these compounds the C atom has a lone pair of electrons, but in each the outer sphere is a complete octet, viz. 4 in uniting C to O or N by a double covalent link, a lone pair and two in attaching O or N to C by a co-ordinate link.

The presence of this lone pair accounts for the fact that these compounds can form additive compounds, e.g. CO gives  $\text{COCl}_2$  with chlorine,  $\text{H} \cdot \text{COONa}$  with NaOH, and the unstable formyl chloride  $\text{H} \cdot \text{C}(\cdot \text{O})\text{Cl}$  with HCl; cf. *Gattermann*, *Synthesis of Aldehydes* (B., 1897, 1622, and p. 492).

For carbylamines cf. Chap. IV, C5. Hydrocyanic acid is a typical tautomeric substance (cf. Chap. XII, A., and LIII, B1):



**Fulminic acid**,  $\text{HC'ON}$ , isomeric with cyanic acid, is usually represented as the oxime of carbonic oxide  $\text{C}^{\text{+}}\text{N}^{\text{-}}\text{OH}$  (*Nef.*, A., 280, 303).

Its mercurous salt which explodes with great violence when heated or struck is largely used in the manufacture of percussion caps, dynamite cartridges, &c., and is made by the action of alcohol and nitric acid on mercuric nitrate.

The structure of the acid is largely based on the following facts: (1) With one equivalent of  $\text{HCl}$  an additive compound is formed which has been shown to be the chloride of form-hydroxamic acid, viz.  $\text{Cl}\cdot\text{CH}:\text{N}\cdot\text{OH}$ . (2) Mercury fulminate is formed by heating the mercury salt of nitro-methane with water:  $\text{CH}_2:\text{NO}\cdot\text{OMe} \rightarrow \text{C}:\text{N}\cdot\text{OMe}$ . (3) With nitrous acid it yields methylnitrolic acid,  $\text{C}:\text{N}\cdot\text{OH} + \text{H}\cdot\text{NO}_2 \rightarrow \text{O}_2\text{N}\cdot\text{CH}:\text{N}\cdot\text{OH}$ .

The free acid prepared from the K salt and excess of sulphuric acid is very volatile and readily polymerizes.

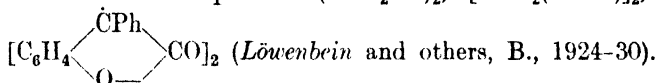
## B. Free Radicals \*

*Waters'* definition is "Free radicals are complexes of abnormal valency which possess additive properties but do not carry electric charges and are not free ions". In another chapter (Ethane, I, A.) it has been pointed out that in reactions in which it is theoretically possible that free radicals might be produced the actual products isolated are compounds formed by the union of two radicals, e.g.  $\text{CH}_3 + \text{CH}_3 = \text{C}_2\text{H}_6$ . It is only within recent years that it has been proved that such radicals containing tervalent carbon can exist in a free form for comparatively short periods of time. The ready dissociation of hexaphenylethane,  $\text{C}_2\text{Ph}_6$ , into triphenylmethyl,  $\text{CPh}_3$  (*Gomberg*, 1900), afforded the first example of the isolation of such a radical. The substance is characterized by its highly unsaturated nature and the readiness with which it forms additive compounds with oxygen, iodine, ethers, &c. More recently the still more intensively reactive alkyl radicals—methyl, ethyl, and benzyl—have been prepared by *Paneth* and his co-workers (1929–36). The method consists in heating lead tetramethyl or an analogous compound in a rapid stream of hydrogen or nitrogen under low pressures (1.5–2 mm.) in a quartz vessel.

\* *Trans. Far.*, 1934, 3, and C. and I., 1939, 579.

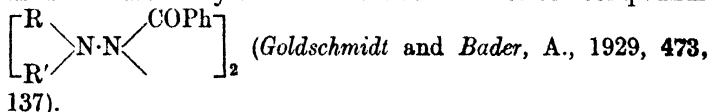
The methyl radical has a mean half-life of 0.006 sec. or 0.1 sec. with an inert gas as carrier and a temperature of 500°. With a quartz vessel the radicals react at the walls forming ethane, with hydrogen they tend to form methane, and with arsenic, antimony, bismuth, and beryllium in mirror form the radicals give the methyl derivatives of these elements and the mirror gradually disappears. At room temperature trimethyl derivatives of arsenic and antimony are formed together with compounds of the type of cacodyl (p. 134), but if the mirrors are heated yellow oils, e.g.  $(\text{AsMe}_2)_2$  and  $(\text{AsMe})_3$ , are obtained. So far free butyl and phenyl have not been observed, but free benzyl has roughly the stability of methyl. Methyl and benzyl are also formed by the thermal decomposition of acetone and dibenzyl ketone.

Intermediate between Me and Et on the one hand and  $\text{CPh}_3$  on the other are the radicals  $(\text{CPh}_2\text{Bu}(\text{tert}))$ ,  $(\text{CPh}_2\cdot\text{C}:\text{CPh})$  and  $(\text{CPh}_2\cdot\text{CHPh}_2)$ , which show reversible change of colour with change of temperature. Similar changes occur with compounds  $(\cdot\text{CPh}_2\text{CN})_2$ ,  $[\cdot\text{CPh}_2(\text{COPh})]_2$ , and



The free radical  $\text{CH}_3\cdot\text{CO}$  formed by exposure of acetone to ultra-violet light has a very short life and yields diacetyl (J. C. S., 1937, 567).

The stability of the radicals is dependent on the simultaneous presence of groups capable of attracting and repelling electrons, as is well shown by a detailed examination of the compounds



Compounds like hexaphenylethane which dissociate readily are characterized by having low heats of dissociation, e.g. 11.5 Kg. cal., as compared with 71 Kg. cal. for less highly substituted ethane compounds, and similarly the heat of dissociation of a compound  $>\text{N}\cdot\text{N}<$  fully substituted is about  $\frac{1}{10}$  of that for a non-dissociating nitrogen compound.\*

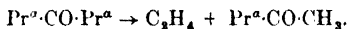
According to Rice and others (J. A. C. S., 1933, 3898, 4329) most organic compounds at 800°–1000° break down in the

\* For general summary of recent work cf. Pearson, Rep., 1934, 240. Free Radicals in Solution, Hey and Waters, Chem. Rev., 1937, 169.



vapour phase by a process of cracking, yielding simple alkyl radicals, e.g. methyl, ethyl. The required energy of activation, about 80,000 cal., is roughly the heat of formation of a C—C link.

Free radicals are also formed by photochemical activation of vapours of aldehydes and ketones, carbon monoxide being liberated. Higher ketones yield olefine and a simpler ketone:



Similar disruptions into free radicals can also occur in liquid phase and in solution, but in the latter case the free radical may react with the solvent, e.g. benzene or paraffin:



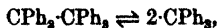
Methylene with a divalent carbon atom is extremely unstable, and where it might be expected carbon is usually deposited, but it is probably formed by the photolysis of ketene (J. C. S., 1933, 1533).

All the above alkyl radicals contain a single free electron; the carbon has in its outer sphere 7 electrons, six utilized in pairs in attaching the three hydrogens and a lone electron, and in this respect they differ from all molecules where, if free electrons are found, they are always in pairs. The presence of a single free electron gives a definite magnetic moment just as in monatomic H. Paramagnetism is regarded as a property characteristic of free radicals (*Kuhn*, 1931).

Free radicals with short lives are formed probably in many photochemical processes, in thermal decompositions and in reactions catalysed by organic peroxides such as the polymerization of styrene, addition of HBr to olefines and the *cis-trans* isomerization of olefines. The conversion of alkyl aryl ethers into phenols at 240°–250°, e.g.  $\text{C}_6\text{H}_5 \cdot \text{O} \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$  into  $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{OH}$ , probably involves the formation of radicals  $\text{C}_6\text{H}_5 \cdot \text{O} \cdot$  and  $\cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$ , as in the presence of quinoline the products include hydroxy-phenyl quinolines and benzyl quinolines.

## 1. TRIPHENYLMETHYL GROUPS OF RADICALS\*

These are of great interest as they are some of the most stable tervalent carbon radicals. In 1900 *Gomberg* (J. A. C. S., 1900, 757), in attempting to prepare hexaphenyl-ethane,  $\text{CPh}_3\cdot\text{CPh}_3$ , by the action of silver or zinc on a benzene solution of triphenylmethyl chloride,  $\text{CPh}_3\text{Cl}$ , obtained a yellow solution from which by evaporation in contact with air a **peroxide**,  $\text{CPh}_3\cdot\text{O}\cdot\text{O}\cdot\text{CPh}_3$ , was isolated. On evaporation in the absence of air an extremely reactive product was obtained, which reacted with iodine forming  $\text{CPh}_3\text{I}$ , with nitric oxide giving  $\text{CPh}_3\cdot\text{N}\cdot\text{O}$ . The product also gave additive compounds with esters, ethers, ketones and certain hydrocarbons (1915, 2569). *Gomberg* suggested that the yellow benzene solution contained the triphenylmethyl radical  $\cdot\text{CPh}_3$  although molecular weight determinations by the cryoscopic method indicated the double formula  $\text{C}_2\text{Ph}_6$ . Since 1900 numerous radicals of the same type have been prepared—some in solution only, others in the solid state. In the great majority of cases the substance contains a tervalent carbon attached to three aryl groups, an aliphyl (branched olefine type) or thienyl ( $\cdot\text{C}_4\text{H}_3\text{S}$ ) or an  $\cdot\text{OAr}$  group. The solid compounds are usually colourless or only very faintly coloured, although a few deeply coloured ones are known; all yield coloured solutions in neutral solvents, varying from yellow to purple-red and tending to increase in depth with rise of temperature. At one time it was suggested that the colourless solid and the freshly prepared colourless benzene solution contained hexaphenyl-ethane whereas the yellow solution obtained on standing contained a quinonoid isomeride, but the examination of naphthalene solutions of hexaphenyl-ethane by the cryoscopic method gave molecular weights much less than that required for  $\text{C}_2\text{Ph}_6$  indicating appreciable dissociation and the isolation of coloured analogues of  $\cdot\text{CPh}_3$  which showed 100 per cent dissociation in solution confirmed *Gomberg's* view that the colour is due to the formation of free radicals of the  $\text{CPh}_3$  type. In solutions therefore there is an equilibrium,



which varies with the solvent and the temperature. The for-

\* Chem. Rev., 1924, 123.

mation of the free radicals accounts for the remarkable reactivity of the yellow solutions with iodine, nitric oxide, oxygen, &c. The equilibrium is destroyed by shaking the yellow solution with air, the  $\text{CPh}_3$  is removed as the peroxide (cf. p. 863) and the solution becomes colourless, but gradually becomes yellow again as more  $\text{CPh}_3$  is formed.

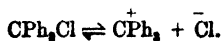
The extent of the dissociation is also largely affected by the aryl groups present; a compound with a  $\cdot\text{C}_6\text{H}_4\cdot\text{C}_6\text{H}_5$  group always dissociates into radicals more readily than one containing  $\cdot\text{C}_6\text{H}_5$ , and a comparison of the three compounds, I  $[\cdot\text{CPh}_2\cdot\text{C}_6\text{H}_4\text{Ph}]_2$ , II  $[\cdot\text{CPh}(\text{C}_6\text{H}_4\text{Ph})_2]_2$ , III  $[\cdot\text{C}(\text{C}_6\text{H}_4\text{Ph})_3]_2$ , shows that in benzene solutions of fixed concentration I is dissociated to the extent of 15 per cent, II to 80 per cent, and III to 100 per cent, and at the same time there is a change in the colours of the solutions from orange-red in I, red in II to violet-red in III. The last also yields dark green crystals indicating dissociation in the solid state. Numerous other cases of dissociation into radicals of the  $\cdot\text{CPh}_3$  type are known, e.g.  $[\text{CPh}_2 \alpha\text{-Nap.}]_2$ ,  $\text{CPh}_3\cdot\text{CPh}_2\text{Me}$ , which dissociates into  $\text{CPh}_3$  and  $\text{CPh}_2\text{Me}$ , and  $[\text{CPh}_3\cdot\text{CPh}_2]_2$ .

The introduction of 3 : 4-methoxy groups or of 3 : 4-methylenedioxy groups renders the radical more stable (J. C. S., 1939, 33, 303, and *Gomberg*, J. A. C. S., 1925, 2392).

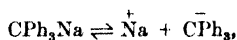
The radicals  $\text{CPh}_2\text{:CH}\cdot\text{CPh}_2$ ,  $(\text{CPh}_2\text{:CH})_2\text{CPh}\cdot$  and  $(\text{CPh}_2\text{:CH})_3\text{C}\cdot$  increase in the order given as regards stability (*Wittig* and *Kosach*, A., 1937, 529, 167).

In all such radicals the outer electron layer of the tervalent C atom is a septet and not the stable octet and comprises six from the 3 covalencies and a *single lone* electron, not the usual pair met with in numerous O, S, N compounds, and in the formation of additive compounds with I, NO and  $\text{O}_2$  the carbon atom attains the stable octet.

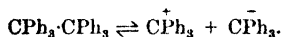
The  $\text{CPh}_3$  radical forms compounds not only with halogens, e.g.  $\text{CPh}_3\text{Cl}$  and  $\text{CPh}_3\text{I}$ , but also with metals, e.g.  $\text{CPh}_3\text{Na}$ . The sodium compound is best prepared by the action of sodium amalgam on  $\text{CPh}_3\text{Cl}$ . Both  $\text{CPh}_3\text{Cl}$  and  $\text{CPh}_3\text{Na}$  are remarkably reactive; the chlorine atom is readily replaced by OH and more resembles the Cl of an acyl chloride than of an aliphyl chloride. Solutions of the chloride in liquid  $\text{SO}_2$  are strong electrolytes due to the dissociation,



Similarly solutions of the sodium compound in liquid ammonia are good electrolytes due to ionization,



and a solution of hexaphenylethane in liquid sulphur dioxide is a conductor due to the formation of  $\text{CPh}_3^\cdot$  and  $\text{CPh}_3^-$  ions,



The dissociation of hexaphenylethane is thus of two types, viz. into the free radicals  $\cdot\text{CPh}_3$  and into the anions and cations  $\text{CPh}_3^-$  and  $\text{CPh}_3^+$ . Both types may occur at the same time so that the equilibrium is a complex one, but on the whole the former occurs in neutral solvents such as benzene or naphthalene and the latter in liquid sulphur dioxide.

The stability of the radical and hence the degree of dissociation of the substituted ethane depends largely upon the complexity of the substituents, e.g. phenyl, naphthyl, diphenyl, &c., and the same holds good in the case of the dissociation of substituted hydrazines, e.g.  $\text{NPh}_2\cdot\text{NPh}_2$ , whereas the compound  $\text{CPh}_3\cdot\text{NPh}_2$  formed by the union of  $\cdot\text{CPh}_3$  and  $\cdot\text{NPh}_2$  radicals is extremely stable and shows no tendency to dissociate.

A physical characteristic of all free radicals is their remarkably high magnetic susceptibility, and *Sugden* (Trans. Far., 1934, 18) recommends this as a convenient test for a free radical.

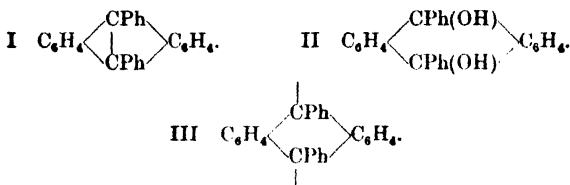
Pentaphenylethane,  $\text{CPh}_3\cdot\text{CHPh}_2$ , tends to dissociate when its anisole solution is heated in absence of air, and on cooling two  $\cdot\text{CHPh}_2$  radicals unite to form *s*-tetraphenylethane.

Other trivalent radicals are  $\cdot\text{CPh}_2\text{OPh}$ ,  $\cdot\text{CPh}_2\cdot\text{ONa}$ ,  $\cdot\text{CPh}(\text{OPh})(\text{ONa})$ , &c. (*Kraus*, J. C. S., 1924, 2196).

It is possible that by the breaking of one of the links of an olefine bond to obtain a compound with two free radicals attached to one another by a covalent link, e.g. ethylene could give  $-\text{CH}_2-\text{CH}_2-$ .

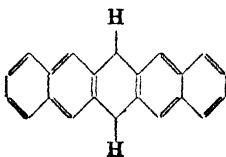
Compounds of this type have been obtained in the anthracene series, e.g. 9:10-diphenylanthracene I (*Ingold and Marshall*, J. C. S., 1926, 3080) in xylene solution is colourless when cold, but the colour deepens on heating. The coloured solution is highly unsaturated and readily adds on 2Na, 2Cl

or 2OH by the action of sodium, chlorine or water; in the latter case the carbinol II is formed indicating the presence of the tervalent C compound III in the coloured solution:



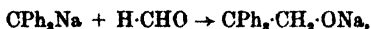
The photochemical activation of anthracene and the formation of dianthracene is due to this type of dissociation.

The 2:3:6:7-dibenzanthracene which is a deep blue compound forming coloured solutions which do not deepen on heating is probably



with two tervalent C atoms.

Compounds of the type sodium triphenylmethyl,  $\text{Na}\cdot\text{CPh}_3$ , are red solids sensitive to oxygen; with water, hydroxylic compounds or aldehydes and ketones which can react in an enolic form, they yield the original hydrocarbons, e.g. triphenylmethane; with  $\text{CO}_2$  acids of the type of triphenylacetic acid, and with methyl iodide hydrocarbons, e.g.  $\text{CH}_3\cdot\text{CPh}_3$ . With aldehydes or ketones incapable of reacting in the enolic forms, the sodium compounds react, yielding alcohols,



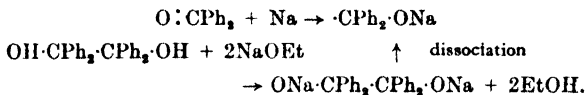
and in many respects resemble *Grignard* reagents, but are much more reactive (*Schlenk* and others, B., 1914, 1664; 1916, 608; 1922, 225), and with acid chlorides or esters of the type of ethyl benzoate they yield ketones, e.g.  $\beta$ -benzopinacolone  $\text{CPh}_3\cdot\text{CO}\cdot\text{Ph}$ .

All the coloured metallic compounds of the type of triphenylmethyl when examined in dry ethereal solution are found to be good conductors of the electric current and are

presumably ionized. Similarly with the coloured sodium compounds like sodium benzyl  $\text{NaCH}_2\cdot\text{C}_6\text{H}_5$  and the additive compound of sodium and stilbene; whereas the colourless compounds lithium phenyl,  $\text{LiPh}$ , &c., in ethereal solution are non-conductors.

## 2. METAL KETYLs

The sodium compounds, e.g.  $\cdot\text{CPh}_2\cdot\text{ONa}$ , are obtained by dissolving the metal in a diarylketone in an indifferent solvent or by the action of sodium ethoxide on a benzopinacolone:

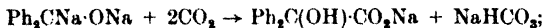


Some are best prepared by double decomposition in dry ethereal solution between the ketyl  $\text{Ph}\cdot\text{C}_6\text{H}_4\cdot\text{CPh}\cdot\text{OK}$  and different ketones, e.g. dimethylpyrone.

All the metal ketyls are highly coloured. They are extremely reactive. Atmospheric oxygen yields the original ketone and an alkali peroxide, iodine yields alkali iodide and ketone, water yields the ketone and the carbinol  $\text{CHR}_2\cdot\text{OH}$ . With excess of sodium the ketyls yield disodium derivatives  $\text{Ph}_2\text{CNa}\cdot\text{ONa}$ ; these are also coloured and react readily with oxygen or water, e.g.



and with carbon dioxide yielding acids of the benzilic series

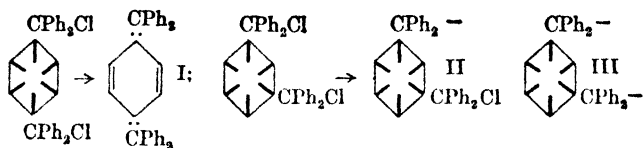


with methyl iodide the methyl ether of a tertiary alcohol is formed  $\text{Ph}_2\text{CMe}\cdot\text{OMe}$ , but this readily decomposes into the olefine  $\text{Ph}_2\text{C}:\text{CH}_2$  and  $\text{MeOH}$ .

Benzaldehyde, ethyl benzoate and phenyl benzoate react with sodium yielding highly coloured metallic derivatives (*Blicke*, J. A. C. S., 1924, 2560; 1925, 229), probably  $\text{Ph}\cdot\text{CH}\cdot\text{ONa}$  and  $\text{Ph}\cdot\text{CHNa}\cdot\text{ONa}$ .

The two isomeric compounds, tetraphenyl-*m*- (and *p*-) xylene dichlorides,  $\text{CPh}_2\text{Cl}\cdot\text{C}_6\text{H}_4\cdot\text{CPh}_2\text{Cl}$ , behave quite differently when treated with metals. The *p*-compound readily yields the *p*-quinonoid compound I (*Thiele* and *Balhorn*, B., 1904, 1463), whereas the *m*-compound loses either one or

both chlorine atoms, yielding the triphenylmethyl derivatives II and III (*Schlenk and Brauns*, 1915, 661). These facts support the view that *m*-quinonoid compounds are incapable of existence.

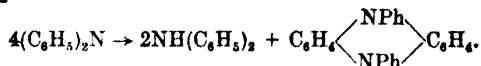


For tervalent Silicon Compounds cf. *Kipping*, J. C. S., 1923, 2832; 1929, 2545.

### Free Radicals containing Bi- and Quadri-valent Nitrogen

*Bivalent*.—According to *Wieland* (B., 1911, 200; 1912, 127; 1913, 233; 1914, 2113) tetraphenylhydrazine, Ph<sub>2</sub>N·NPh<sub>2</sub>, dissociates to the extent of 10 per cent in benzene and 20 per cent in nitrobenzene, giving coloured solutions of great reactivity and, in the absence of air, yielding the following products: with nitric oxide diphenylnitrosamine NPh<sub>2</sub>·N:O, with sodium the compound NPh<sub>2</sub>Na, with triphenylmethyl triphenylmethyldiphenylamine CPh<sub>3</sub>·NPh<sub>2</sub>, pointing to the presence of the free radical NPh<sub>2</sub> which may be regarded as comparable with N:O.

When the benzene solution of tetraphenylhydrazine is boiled the products are diphenylamine and diphenylhydrophenazine, C<sub>6</sub>H<sub>4</sub> < NPh > C<sub>6</sub>H<sub>4</sub>, formed by the condensation of four NPh<sub>2</sub> radicals:



Negative groups such as NO<sub>2</sub> militate against dissociation, whereas Me, OMe, and NMe<sub>2</sub> groups facilitate dissociation, as shown by molecular weight determination.

Probably in these hydrazines, as in the triphenylmethyl compounds, not only is there equilibrium between the radicals

and their polymers but also between benzenoid and quinoid

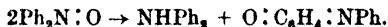
forms, e.g.  $\text{PhN}:\text{C}_6\text{H}_4 \begin{smallmatrix} \text{H} \\ \diagup \end{smallmatrix}$ ,  $\text{PhN}:\text{C}_6\text{H}_4 \begin{smallmatrix} \text{H} \\ \diagup \\ \text{NPh}_2 \end{smallmatrix}$ .

Compounds of the type  $\text{NR}_2\cdot\text{NR}\cdot$  also appear capable of existence (*Goldschmidt*, B., 1920, 44; 1922, 616; A., 1924, 437, 194). They are termed **hydrazyls** and one of the most interesting is *αα*-diphenyl-*β*-picrylhydrazyl,  $\text{NPh}_2\cdot\text{N}\cdot\text{C}_6\text{H}_2(\text{NO}_2)_3$ , a stable crystalline solid with a colour similar to that of potassium permanganate; hydroquinone reduces it to the colourless hydrazine and the colour change is so sharp that the free radical can be estimated by titration with standard hydroquinone solution.

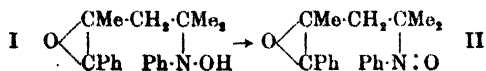
*Quadrivalent Nitrogen*.—Tetraethylammonium,  $\text{NEt}_4$ , is obtained as a blue liquid by electrolysing a solution of its iodide in liquid ammonia and combines with great readiness with iodine.

## Quadrivalent Nitrogen or Monovalent Oxygen

By the action of silver oxide on *ββ*-diphenylhydroxylamine,  $\text{Ph} \begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix} \text{N}\cdot\text{OH}$ , an atom of hydrogen is removed and diphenylnitric oxide,  $\text{Ph}_2\text{N}:\text{O}$ , is formed and exists in this form in solution. Like nitrogen peroxide,  $\text{NO}_2$ , it is very reactive, e.g. liberates iodine from acidified potassium iodide, is reduced by phenylhydrazine to diphenylhydroxylamine and by stronger reducing agents to diphenylamine. Dilute hydrochloric acid converts it into a mixture of diphenylamine and quinoneanil:

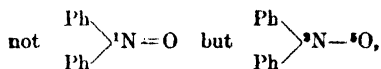


*Kenyon* and others (J. C. S., 1926, 1612; 1932, 170) have obtained red compounds II by the action of silver oxide on a product formed by condensing *β*-phenylhydroxylamine and acetone, viz. I:





These compounds exhibit paramagnetism. It has been suggested that these compounds contain quadrivalent nitrogen, but as this would give the N atom an outer shell of 9 electrons it is more probable that they contain an atom of univalent oxygen, e.g.

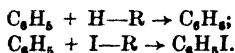


in which the N has an outer octet and the O a septet.

Other compounds containing univalent oxygen are formed by the action of silver oxide on phenols, e.g. guaiacol (*Goldschmidt*, A., 1924, **436**, 202).  $\text{MeO}-\text{C}_6\text{H}_4-\text{O}-$ , and their solutions are highly coloured. A blue phenanthrene radical  $\text{C}_6\text{H}_4-\text{CCl}$

$\begin{array}{c} | \\ \text{C}_6\text{H}_4-\text{C}=\text{O} \end{array}$  exists to the extent of 70 per cent with its polymer in solutions at the ordinary temperature.

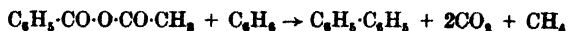
The presence of free radicals (e.g. phenyl) by the decomposition of aromatic diazo-compounds has been rendered probable by *Waters* (1937). Thus benzenediazoacetate,  $\text{C}_6\text{H}_5\cdot\text{N}:\text{N}\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ , in the form of its tautomer nitrosoacetanilide, yields with *n*-hexane, cyclohexane, ether or acetone a certain amount of benzene, and with methyl or ethyl iodides a certain amount of iodobenzene:



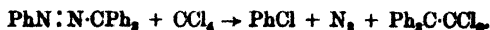
Aliphatic diazo-compounds behave in a somewhat similar manner; thus keten is formed from diazomethane and carbon monoxide:



also acetyl benzoyl oxide with benzene gives diphenyl-methane and  $\text{CO}_2$ :



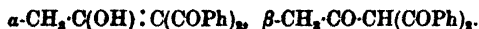
and



## LIH. TAUTOMERISM \*

Attention has already been drawn to certain compounds, such as isatin, ethyl acetoacetate, &c., which react as though they had two different structures. *Kekulé* himself, 1870, suggested that the existence of only one form of each ortho-substituted benzene derivative could be explained by a rapid oscillation between the two possible forms. In 1877 *Butleroff* suggested that HCN and HCNO might be equilibrium mixtures, and in 1878 *Erlenmeyer* pointed to the fact that aldehydes and ketones are formed in reactions where  $\alpha\beta$ -unsaturated alcohols might be expected (p. 91), and suggested that the latter may pass over into the carbonyl compounds at their moment of formation. *Baeyer* (1882-83) drew attention to the dual nature of isatin, and *Laar* (B., 1885, 648; 1886, 730), in a comprehensive survey of all such compounds, including isatin, ethyl acetoacetate, *p*-nitrosophenyl (= quinone monoxim),  $\alpha$ -naphthaquinone phenylhydrazone (= benzeneazo- $\alpha$ -naphthol), suggested that the mobile H atom on which the possibility of isomerism depends occupies a position intermediate between its position in the two isomers. *Laar* introduced the name **tautomerism**, but several others have been suggested such as desmotropism (= change of bonds), dynamic isomerism (*Lowry*), but *Laar's* term is the one generally used.

In 1896 *Claisen* obtained two distinct crystalline forms of acetyldibenzoylmethane,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}(\text{COPh})_2$ , both of which had the same molecular weight in benzene solution. The  $\alpha$ -form, m.-pt.  $81^\circ$ - $85^\circ$ , is readily soluble in sodium carbonate solution, and gives an intensely coloured iron salt with ferric chloride, whereas the  $\beta$ -form, m.-pt.  $107^\circ$ - $110^\circ$ , gives neither of the above reactions, but on prolonged contact with sodium hydroxide solution it dissolves, and on the careful addition of acid the  $\alpha$ -compound is precipitated, and *Claisen* suggested the alcoholic (enolic) form for the  $\alpha$ - and the ketonic structure for the  $\beta$ -compound:



He was able to show that either form when heated in alcoholic solution or when fused in the absence of a solvent gives

\* *Tautomerism*, J. W. Baker, London, 1934.

products from which both  $\alpha$ - and  $\beta$ -compounds can be isolated. Other  $\beta$ - $\alpha$ -ketones or ketonic esters behave similarly, and in all such cases there are two distinct substances, the keto and the enol, each capable of changing into the other and often existing side by side in a state of equilibrium, but if a reagent is present which can react with the one form only, the equilibrium is disturbed and the non-reactive form changes over into the reactive until the whole consists of this or of its derivative. In the case mentioned above the change is comparatively slow and can be studied, and each of the two isomers can be isolated in a pure form. If, however, the change is extremely rapid, then it will be possible to isolate the one form only, e.g. isatin and hydrogen cyanide.

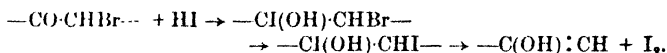
### A. Keto-enolic Type

In 1911 *Knorr* (B., 1138) succeeded in obtaining ethyl acetoacetate in two distinct modifications, and was able to confirm the conclusion that the ordinary liquid ester is an equilibrium mixture of the keto and enol forms—a conclusion based on the study of certain physical constants (Chap. LXXI).

By cooling to  $-78^{\circ}$  a solution of the ordinary ester in alcohol and ether in an apparatus specially designed to exclude moisture and to maintain a high vacuum *Knorr* isolated the ketonic form as well-defined needles or prisms, m.-pt.  $-39^{\circ}$  and b.-pt.  $39^{\circ}$ – $40^{\circ}/2$  mm. It does not give a coloration with ferric chloride, and does not react with bromine solution. Even at the ordinary temperature it takes several weeks before the equilibrium mixture is again formed in the absence of catalysts, but traces of HCl or  $\text{FeCl}_3$  bring about equilibrium in a few seconds. The practically pure enol is obtained by suspending the sodium derivative in light petroleum cooled to  $-78^{\circ}$  in a special apparatus, and passing in hydrogen chloride just insufficient for complete decomposition. The solution when filtered and evaporated at  $-78^{\circ}$  yields the enolic ester as a colourless oil, which gives an intense coloration with ferric chloride. At the ordinary temperature it requires ten to fourteen days to again form the equilibrium mixture, but at  $100^{\circ}$  the change is completed in one minute. By comparing the refractive index of the ordinary ester with the values for mixtures of known concentration, it has been calculated that

the equilibrium mixture contains 7 per cent of the enol (cf. *Meyer and Willson*, B., 1914, 837).

A chemical method for estimating enols in equilibrium mixtures is due to *K. H. Meyer* (A., 380, 212; B., 1911, 2718; 1912, 2843). The enolic modification reacts instantaneously with an alcoholic solution of bromine, yielding an unstable dibromide, which immediately gives off hydrogen bromide and forms the bromo-ketone. The best method for estimating the amount of enol is to add an excess of the alcoholic bromine solution, to remove the excess by means of  $\beta$ -naphthol, and then to determine the amount of bromo-ketone by adding potassium iodide solution, and titrating the liberated iodine by means of standard thiosulphate:



In this way it has been shown that the ordinary ethyl acetoacetate contains about 7 per cent of the enol, and the same results are obtained when freshly prepared solutions in various solvents are examined; but such solutions, when kept, undergo change, e.g. a hexane solution when kept for forty-eight hours at 18° contains nearly equal amounts of keto and enolic modifications. A rise in temperature also tends to favour the formation of the ketonic form. In a similar manner acetylacetone has been shown to contain 80 per cent of enol. By using this bromine method it is found that during slow distillation (6–8 drops per minute) of acylacetic esters the distillate contains much enol, whereas the proportion of keto to enol in the residue remains constant. This leads to the conclusion that enolization occurs in the vapour phase (*Ann. Chim.*, x, 1932, 18, 81). By using quartz vessels it is possible to obtain a distillate of pure enol and a residue of pure keto form.

Solid crystalline forms are not equilibrium mixtures, but consist of the one modification only and the mixture is formed on solution (B., 1912, 2843). In alcoholic solution acetaldehyde, acetone, pyruvic acid, and acetophenone exist almost entirely in the ketonic form, even when sodium ethoxide is present. In compounds containing methylene attached to two COX groups where X = H, Me, Ph, OH, OMe, OEt, NHPh, CO<sub>2</sub>Me, and CO<sub>2</sub>Et, the following is the relative order of the enolizing effect of the radical X: OMe, OEt, OH, NHPh,

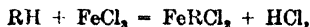
Me, Ph,  $\text{CO}_2\text{Et}$ ,  $\text{CO}_2\text{Me}$ . Ethyl malonate exists almost entirely in the keto form and the sodium derivative has the enolic structure,  $\text{CO}_2\text{Et}\cdot\text{CH}:\text{C}(\text{ONa})\cdot\text{OEt}$ , but when acidified the enolic modification changes rapidly to the keto form.

The solvent has a marked effect upon the equilibrium; thus the percentage of enolic form in solutions of methyl benzoylacetate,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{Me}$ , is as follows: water, 0.8; methyl alcohol, 13.4; chloroform, 15.4; hexane, 69; and the same solvent has much the same effect on different tautomeric substances. The reaction with bromine appears to be unaffected by light, and in this respect differs from ordinary bromine substitutions and from the addition of bromine to unsaturated  $\alpha\beta$ -acids (p. 820).

*Kaufmann* and *Richter* (B., 1925, 216) show that the capacity to add bromine is not a characteristic property of all enols as it may be suppressed by steric influences or by the presence of acylous groups.

Other methods of estimating enols in allelotropic mixtures are:

(a) A colorimetric method based on the reaction between the enol and ferric chloride,



where R is the enolic residue. The comparison is made with standard solutions prepared by mixing solutions of the pure enol with one of sublimed ferric chloride in molecular proportions. For exceptions see B., 1925, 216, and 1560.

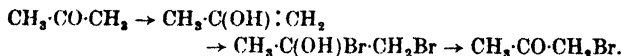
(b) **Ozone** (*Scheiber* and *Herold*, A., 1914, 405, 296). This reagent has no enolizing action on the keto-enolic equilibrium mixture and immediately transforms the enol into an ozonide (Chap. XLVIII, G.), but does not attack the keto form. By examining and estimating the products formed by the action of water on the ozonide the structure of the enolic form and a rough estimate of the amount present can be ascertained. In most cases the results confirm those arrived at by other methods. In the case of benzoylacetone where isomeric enolic forms are possible, the results show that in chloroform solution it exists mainly as  $\text{C}_6\text{H}_5\cdot\text{C}(\text{OH})\cdot\text{CH}\cdot\text{CO}\cdot\text{CH}_3$ , as the products formed from the ozonide are benzoic acid and methyl-glyoxal  $\text{CHO}\cdot\text{CO}\cdot\text{CH}_3$ . The results with oxalacetone,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CO}_2\text{Et}$ , indicate the presence of two mono-enolic and one

di-enolic form, viz.  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}:\text{C}(\text{OH})\cdot\text{CO}_2\text{Et}$ ,  $\text{CH}_3\cdot\text{C}(\text{OH})\cdot\text{CH}\cdot\text{CO}\cdot\text{CO}_2\text{Et}$  and  $\text{CH}_3\cdot\text{C}(\text{OH})\cdot\text{C}:\text{C}(\text{OH})\cdot\text{CO}_2\text{Et}$  (cf. also B., 1914, 2704).

In all cases where the composition of the equilibrium mixture is determined by the action of chemical reagents and not from a study of physical constants, the possibility of the enolizing action of the reagent employed must be borne in mind. It is claimed that substances such as bromine and ozone have no enolizing effects, and hence the conclusions derived from the reactions should agree with those based on physical constants. On the other hand, it is well known that alkalis have a considerable enolizing effect,\* and the sodium derivatives of esters which can react as tautomerides are usually represented as derived from the enolic forms.

Ultra-violet absorption curves indicate a small amount of enol present in acetaldehyde (C. R., 1927, **184**, 1452).

Enolization of simple aldehydes and ketones can also take place in the presence of certain reagents. Thus the sodium derivatives of ketones or aldehydes (p. 161) are represented as enolic compounds (*Freer*). *Grignard* reagents favour enolization of  $\beta$ -ketonic esters (*Grignard*, C. R., 1902, **134**, 849; *Hepworth*, J. C. S., 1919, 1205), and can produce enolization in ordinary aldehydes and ketones (*Bhagvat* and *Sudborough*, J. I. I. S., 1919, 187). On the other hand,  $\text{ZnEtI}$  can be used for estimating the enol (Bull. Soc., 1923, **33**, 1414). According to *Lapworth* (J. C. S., 1904, 30), the bromination of a ketone is preceded by the enolization of the ketone, the enol then forms an additive compound with bromine, and hydrogen bromide is finally eliminated,

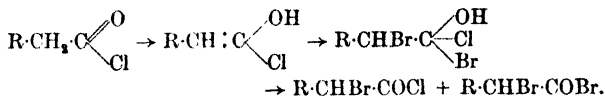


*Dawson* (*ibid.* 1909, 1860; 1912, 1503; 1914, 387, 532) claims that similar reactions take place during the bromination of aldehydes and the presence of mineral acids accelerates the bromination by increasing the rate of enolization.

*Aschan* (B., 1912, 1913; cf. *Smith* and *Lewcock*, *ibid.* 2358; *Ward*, J. C. S., 1922, 1161) concludes that the same

\* The enolizing effect of traces of alkali is well shown in the case of dibenzoylacetylmethane. The m.-pt. of the compound when determined in Jena glass tubes is  $149^\circ$ – $150^\circ$ , but in soft glass tubes falls to  $107^\circ$ – $110^\circ$  owing to traces of alkali in the soft glass producing partial enolization (*Dieckmann*, B., 1916, 2203).

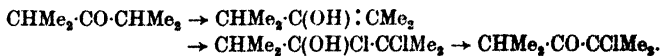
generalizations hold good for the bromination of acids by the *Hell-Volhard-Zelinsky* method (p. 194), as the result of brominating an acid chloride is a mixture of the acid chloride and acid bromide of the  $\alpha$ -bromo-acid,



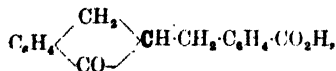
The argument, however, is not conclusive, as similar results might be produced by direct substitution. The conversion of acetyl chloride into acetyl bromide by means of hydrogen bromide and the converse change are also probably due to the intermediate formation of an additive compound between the enolic form and the halogen hydride.

*Meyer* (*ibid.* 2864) has been able to show that the reaction between bromine and malonic acid is uni- and not bi-molecular, as it should be if the reaction is one of direct substitution. The fact that the reaction is uni-molecular, and independent of the concentration of the bromine, is in complete harmony with the view that the reaction actually measured is the enolization  $\text{CO}_2\text{H} \cdot \text{CH}_2 \cdot \text{COOH} \rightarrow \text{CO}_2\text{H} \cdot \text{CH} : \text{C}(\text{OH})_2$ , and that the subsequent reactions are extremely rapid compared with this.

*Favorski* (Abs., 1913, i, 12) shows that  $\text{PCl}_5$  and  $\text{PBr}_5$  produce enolization in the case of certain ketones. The normal reaction with  $\text{PCl}_5$  consists in replacing O by  $\text{Cl}_2$ ,  $\text{R} \cdot \text{CO} \cdot \text{R}' \rightarrow \text{R} \cdot \text{CCl}_2 \cdot \text{R}'$ . In the case of di-isopropyl ketone, however, the chief product is isopropyl- $\alpha$ -chloroisopropyl ketone,  $\text{CHMe}_2 \cdot \text{CO} \cdot \text{CClMe}_2$ , probably formed by the following series of reactions:

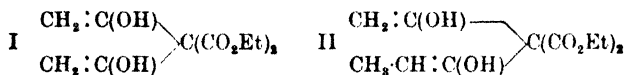


It is possible that the bromination and chlorination of *all* aldehydes, ketones and acids is not preceded by enolization: *Leuch's* observation (B., 1913, 2435) that in the bromination of *d*- $\beta$ -carboxybenzyl- $\alpha$ -hydrindone,



although the monobromo derivative, obtained by replacing the H atom of the CH group by bromine, is mainly the racemic compound, yet possesses a rotation denoting the presence of 10 per cent of the *d*-bromo derivative, *may* indicate that the whole of the bromine compound has not been formed through the intermediary of the enolic compound, as the formation of this compound would destroy the asymmetry of the molecule, and hence the optical activity. *Lapworth* (P., 1913, 29, 289) concludes that the bromination may have been entirely by means of the enolic compound, and that the small amount of *d*-bromo-acid is due to an asymmetric synthesis (Chap. LXXI, 15) from the enol in the presence of the unchanged optically active keto form.

It has been suggested that in certain cases of keto-enolic tautomerism the hydrogen required to produce the hydroxy group does not come from CH or CH<sub>2</sub> between two CO groups. Thus *Brühl* represented ethyl diacetyl-malonate by the enolic formula I, in which the hydrogen



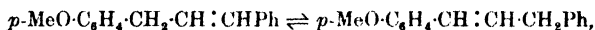
is derived from a terminal CH<sub>3</sub> group. This has been shown by *Auwers* and *Auffenberg* (B., 1917, 929) to be incorrect. The monoacetyl derivative has the normal enolic structure CH<sub>3</sub>·C(OH):C(CO<sub>2</sub>Et)<sub>2</sub>, and when further acetylated gives the O-acetyl derivative CH<sub>3</sub>·C(OAc):C(CO<sub>2</sub>Et)<sub>2</sub>, which is identical with *Brühl's* compound. The proof of the structure of the compounds is largely based on the fact that two different products are formed (a) by first introducing acetyl and then propionyl, (b) by first introducing propionyl and then acetyl, whereas, according to *Brühl's* scheme the two products should be identical, viz. II.

## B. Types of Tautomerism

The term tautomerism now covers all cases in which balanced actions arise from the interconversion of isomerides; thus on the one hand we have isatin which exists in the one



form only and  $\psi$ -nitro-camphor which passes instantaneously into the normal compound, and on the other the change,



which is extremely slow and only brought about with the aid of powerful reagents, e.g. NaOEt at  $85^\circ$ .

The types met with are grouped as follows:

(1) Dyad system, e.g. hydrogen cyanide and acetylene, only 2 atoms in the system.

(2) Triad system,



where A, B and C represent three atoms of polyvalent elements:

(3) Pentad system.

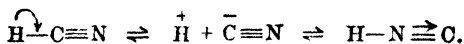
(4) Ring-chain system with mobile H.

(5) Valency tautomerism.

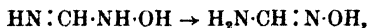
### 1. DYAD SYSTEM

**Hydrogen Cyanide,**  $\text{H}-\text{C}\equiv\text{N} \rightleftharpoons \text{H}-\text{N}\equiv\text{C}$ .—Many attempts have been made to elucidate the structure of this compound and of its derivatives, e.g. metallic cyanides, nitriles, carbylamines, cyanates, and the corresponding sulphur compounds.

For hydrogen cyanide we have the equilibrium,



With HCl, EtOH and  $\text{NH}_2\text{OH}$  it forms respectively iminoformyl chloride (formimido chloride),  $\text{H}\cdot\text{N}:\text{CH}\cdot\text{Cl}$ , formimidoethyl ether,  $\text{HN}:\text{CH}\cdot\text{OEt}$ , and formamido-oxime:



indicating that addition occurs at the C atom only and pointing to the structure  $\text{H}-\text{N}\equiv\text{C}$ .

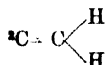
Physical methods for determining the structure have also been applied, but the results are inconclusive. According to *Dadiou* (B., 1930, 251, 1657; 1931, 358) the *Raman* spectrum favours the nitrile structure with only 0.3 per cent of the isonitrile.

The ionized metallic cyanides, whether of normal or iso-structure, give the common ion  $\text{C}^-\equiv\text{N}$ .

It has been suggested that acetylene may be tautomeric in much the same manner as hydrogen cyanide:



a view which has received some support from the fact that certain dihalogen derivatives have the structure  $\text{C}=\text{CBr}_2$  (Lawrie, J. A. C. S., 1906, 489) as on oxidation of the addition compound with HI, viz.  $\text{CBr}_2:\text{CHI}$  dibromoacetic acid  $\text{CHBr}_2\cdot\text{CO}_2\text{H}$  is formed. Physical evidence, however, does not confirm this structure as di-iodoacetylene has a very small dipole moment, and hence presumably has the symmetrical structure. In the normal structure each carbon atom has the stable octet of electrons, whereas in the iso-structure one carbon has a sextet only, including the pair of unshared electrons,



## 2. TRIAD SYSTEM

General expression,  $\text{A}:\text{B}\cdot\text{CH} \rightleftharpoons \text{HA}\cdot\text{B}:\text{C}$ .

(a) **Three carbon system**, where A, B and C all represent carbon atoms. Cases studied in some detail are:



The two compounds are relatively stable as salts, but with alkali (alcoholic NaOEt) an equilibrium mixture is formed (J. C. S., 1931, 1666).

(ii) Substituted diphenylpropene system, e.g. the *p*-methoxy compound, can exist in two forms,  $\text{OMe}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}:\text{CHPh}$  and  $\text{OMe}\cdot\text{C}_6\text{H}_4\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\text{Ph}$ , which are relatively stable, but under certain conditions, e.g. NaOEt at  $85^\circ$ , an equilibrium mixture of the two is formed (J. C. S., 1922, 2381; 1929, 447).

(b) **Keto-enol system**,  $>\text{CH}\cdot\text{C}:\text{O} \rightleftharpoons >\text{C}:\text{C}\cdot\text{OH}$ , with two carbon and one oxygen (cf. this Chap., A.).

(c) **Imino-enamine system**, with two carbons and one nitrogen,  $>\text{CH}\cdot\text{C}:\text{NR} \rightleftharpoons >\text{C}:\text{C}\cdot\text{NHR}$ .

(d) **Methyleneazomethine system**, also two carbons and one nitrogen,  $>\text{CH}\cdot\text{N}:\text{CR} \rightleftharpoons >\text{C}:\text{N}\cdot\text{CHR}$ .

(e) **Amido-amidol system**, with one carbon, one oxygen and one nitrogen,  $\text{NH}\cdot\text{C}:\text{O} \rightleftharpoons \text{N}:\text{C}\cdot\text{OH}$ , the ordinary lactam-lactim tautomerism (cf. p. 520).

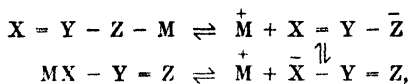
(f) **Amidine system**, with one carbon and two nitrogen atoms,  $\text{NH}\cdot\text{C}:\text{NR} \rightleftharpoons \text{N}:\text{C}\cdot\text{NHR}$ .

*Ingold* (J. C. S., 1923, 1717) has drawn attention to the similarity between these types of tautomerism and various additive reactions, the main difference being that in the latter the addenda are derived from a different molecule and in the former from the same molecule, e.g.  $\text{A}:\text{B} \xrightarrow{+\text{HX}} \text{AH}\cdot\text{BX}$  and  $\text{A}:\text{B}\cdot\text{CH} \rightarrow \text{AH}\cdot\text{B}:\text{C}$ .

System (a) is compared with the *Michael* addition,  $\text{RH} + \text{C}:\text{C} \rightarrow \text{RC}\cdot\text{CH}$ ; system (b) to the aldol reaction (Chap. IX, C.),  $\text{RH} + \text{C}:\text{O} \rightarrow \text{RC}\cdot\text{OH}$ ; systems (c) and (d) to the *Thorpe* reaction,  $\text{RH} + \text{C}:\text{N} \rightarrow \text{RC}:\text{NH}$ ; system (e) to the aldehyde ammonia addition, and system (f) to the hydrobenzamide formation,  $\text{NH} + \text{C}:\text{N} \rightarrow \text{N}\cdot\text{C}\cdot\text{NH}$ .

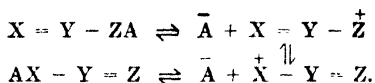
**Ionization and Tautomerism.**—The ease with which many tautomeric compounds yield stable metallic and alkyl derivatives points to a similarity to phenols and acids, i.e. to ionizable compounds. *Goldschmidt* and *Messler* (1890) were the first to suggest that ions play a part in tautomeric changes occurring in the presence of electrolytes, e.g. the formation of sodium compounds, and subsequently *Walden* (1891) and *Mulliken* (1893) proved that compounds of the ethyl acetoacetate type have measurable but small electrical conductivities, but that ethyl *o*-nitrobenzoylmalonate,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{CH}(\text{CO}_2\text{Et})_2$ , has the properties of a strong monobasic acid. These views were accepted by *Knorr* and by *Wislicenus* (1898) in their reviews of tautomeric phenomena. At the present time all tautomeric changes of the triad type are regarded as primarily ionic, and only after release of a cation or an anion does molecular rearrangement occur in the complex anion or cation so formed. *Lowry* (1905) suggested the term **ionotropy** to embrace all such changes, and later *Ingold* (Rep., 1927, 106) advocated the use of **cationotropy** for all cases where a simple cation is eliminated and the change occurs in the relatively complex anion. The most common type of cationotropy is the elimination of a proton ( $\text{H}^+$ ), and all cases of this type can be grouped under the heading **prototropy**. Cases where a simple anion is eliminated and the

change occurs in the resulting cation are grouped together under the term **anionotropy**. This type is far less general than the cationotropic type, and its study dates from 1928. For cationotropy the general expression is:



where X, Y and Z are polyvalent elements and M a univalent metal atom. By replacing M by H the prototropic type is formed.

For anionotropy,



When  $k_1$  and  $k_2$  represent the velocity constants of the direct and reverse reaction, then  $k_1 + k_2$  denotes the *mobility* and  $k_1/k_2$  the *equilibrium*.

**Mobility.**—For a reversible reaction of the 1st order,

$$k_1 + k_2 = 1/t \log_e \{\epsilon/(\epsilon - x)\},$$

where  $x$  is the change of the original tautomer at time  $t$  and  $\epsilon$  is the value of  $x$  at equilibrium.

The factors which affect mobility may be either *internal* or *external*.

*Internal factors*, i.e. structural factors. One of the most important is the presence of a group or groups with a high affinity for electrons, e.g. the ammonium ion  $\overset{+}{N}R_3$  and the carbonyl group,  $R-\overset{\overset{|}{\text{O}}}{\text{C}}=\text{O}$ . Another important factor is the

provision of a suitable seat for the residual negative charge on the anion left after removal of a proton. The  $\overset{+}{R}_3N$  group fails in this respect as compared with carbonyl (*Ingold*, J. C. S., 1931, 1666). In the carbonyl group,  $C \rightarrow \overset{\curvearrowright}{O}=\overset{\overset{|}{\text{O}}}{O}$ , the inductive effect (Chap. XXXV) assists the ionization of a hydrogen atom in an adjacent methylene group and at the same time the more important electromeric effect not only assists ioniza-



$\pm I$  effects are smaller, but the  $\pm T$  effects are much the same as in the  $\alpha$ -position.

*External factors.* The dielectric constant of the medium, i.e. its ionizing power, is an important factor in determining the mobility of the system and catalysts can also facilitate mobility; for prototropic systems the most effective are  $\bar{O}H$  and  $\bar{O}Et$ , which are strongly proton attracting. The order of decreasing catalytic effects for the alkoxide ions is  $\bar{O}Bu$  (tert.),  $\bar{O}Pr$  (iso),  $\bar{O}Pr$  (n),  $\bar{O}Et$ ,  $\bar{OMe}$  (cf. J. C. S., 1929, 447; 1930, 968).

**Equilibrium.**—The effects of various groups in different positions have been examined in the three carbon triad prototropic system:

	$\alpha$ - position	$\beta$ - position	$\gamma$ - position
$\alpha\beta$ -compound favoured ..	$-I, -T$	$+I$	$+I$
$\beta\gamma$ -compound favoured ..	$+I$	$-I, -T$	$-I, -T$

Among external factors temperature and nature of solvent are important. Solubility also plays an important part. For the keto-enol type the following holds for all solvents:

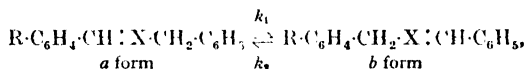
$$\frac{C_e}{C_k} \times \frac{L_k}{L_e} = \text{constant},$$

where  $C_e$  and  $L_e$  are respectively the concentration at equilibrium and the solubility of the enol in the given solvent, and  $C_k$  and  $L_k$  are the corresponding values for the ketone. For a 2 per cent sodium chloride solution of ethyl acetoacetate the value is  $0.4/99.6 \times 11.6/0.5 = 0.09$ . For a solvent in which both forms are equally soluble the ratio is represented by the actual concentrations.

For determining concentrations both physical (Chap. LXXI) and chemical methods can be utilized. For precautions when using chemical methods cf. this Chap., A. The common method for keto-enol tautomers is *Meyer's* bromine method. A reaction of a somewhat similar type has been used for estimating the amount of  $\beta\gamma$ -unsaturated acid or ester in a mixture with the tautomeric  $\alpha\beta$ -compound, as the latter reacts remarkably slowly with bromine and hence the amount of bromine used gives a measure of the  $\beta\gamma$ -compound present in the mixture (*Linstead*, 1927).

*Schoppe* and others (J. C. S., 1930, 968; 1931, 1225) have

made a study of  $\alpha\gamma$ -diphenylpropene systems and  $\alpha\gamma$ -diphenyl-methyleneazomethine systems,



where X = CH or N and R = NR<sub>3</sub>, NH<sub>2</sub>, Me, OMe, I, H, Br and Cl.

For relative increasing mobilities the order in both cases, i.e. X = C(CO<sub>2</sub>Et) and N is the same, viz. NMe<sub>2</sub>, Me, OMe, I, Br, Cl, which corresponds with increasing order of +I effect as indicated by dipole moments.

A comparison of the above compounds with the above substituents (and also NO<sub>2</sub>) in the *meta*- and *para*-positions shows that the *m*-compound have much greater mobilities than the isomeric *p*-compounds. The ratio, however, is not fixed, but falls from 11.2 for NMe<sub>2</sub> to 1.1 for I.

When equilibria are examined the order for decreasing amount of the *a* form is as follows: NMe<sub>2</sub>, OMe, I, H, Br, Cl, Me. This proves that the tautomeric change is not primarily due to the I factor as the above order starts with strong +I, diminishes, and finishes with -I. All the intermediate groups are of the type +I, +T, and the T factor appears to be the important factor controlling equilibrium. The conclusion has been drawn that, as +T favours availability of electrons, the important stage in the change (tautomeric) is the reassociation and not dissociation (*Baker*, pp. 88-91).

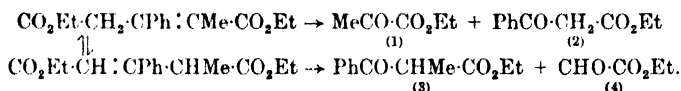
### 3. PENTAD SYSTEM

The common pentad type is that in which a -CO<sub>2</sub>H, CO<sub>2</sub>Et, or COMe group is introduced into the three carbon triad type, e.g. CH<sub>3</sub>·CH:CH·CO<sub>2</sub>Et. These are often regarded as the triad type, but are really pentad systems as the carbonyl also affords a seat for the negative charge. A group of compounds which has attracted much attention is the glutaconic acid group, Δ<sup>1</sup>-propene-1:3-dicarboxylic acid, CO<sub>2</sub>H·CH:CH·CH<sub>2</sub>·CO<sub>2</sub>H. *Thorpe* (1913) concluded that this acid had a symmetrical structure, CO<sub>2</sub>H·CH·CH·CH·CH·CO<sub>2</sub>H, as its 1- and 3-



monosubstituted derivatives appeared to be identical, and also the 1:2- and 1:3-dimethyl acids. Subsequent work by

*Kon, Linstead* and others has shown that the substituted glutamic acids behave as true tautomeric compounds and that the passage from the  $\alpha\beta$ - to the  $\beta\gamma$ -structure occurs under the influence of certain reagents, and that the various isomers are all true ethenoid compounds derived from either  $\text{CO}_2\text{H}\cdot\text{CR}:\text{CH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  or  $\text{CO}_2\text{H}\cdot\text{CHR}:\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ , and in either *cis* or *trans* configurations. The resolution of 1:3-dimethylglutaconic acid into optical antipodes at once demonstrated the impossibility of the symmetrical structure of this acid. The mobility of the glutamic acid system was demonstrated by *Feist* who showed that the products of ozonolysis of ethyl  $\alpha$ -methyl- $\beta$ -phenyl-glutaconate are ethyl pyruvate (1), ethyl benzoylacetate (2), ethyl  $\alpha$ -benzoylpropionate (3), and ethyl glyoxylate (4) (isolated as oxalic acid).

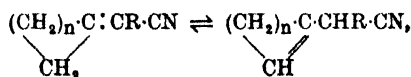


In the case of  $\alpha$ -benzyl- $\beta$ -methyl glutaconic acid the four ethyl esters *cis*- $\alpha\beta$ , *trans*- $\alpha\beta$ , *cis*- $\beta\gamma$ , and *trans*- $\beta\gamma$  have all been isolated.

The compound ethyl 3-methyl- $\Delta^2$ -cyclopropene-1:2-dicarboxylate (I) shows no tendency to pass over to the possible tautomeric form II.



A pentad system containing nitrogen is found in the tautomerism of  $\alpha\beta$ - and  $\beta\gamma$ -unsaturated nitriles, e.g. allyl cyanide  $\rightleftharpoons$  crotononitrile (cf. p. 882), where the  $\alpha\beta$  form is the more stable. The same applies to cyclic unsaturated nitriles,



where as much as 90 per cent of the  $\alpha\beta$  form is present in the equilibrium mixture (Kon, Rep., 1932, 136).



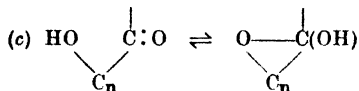
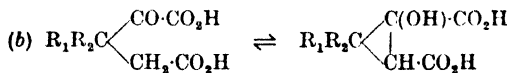
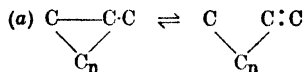
## 4. RING-CHAIN SYSTEM

This is the name given to a tautomeric system where the one form is cyclic and the other acyclic. The various types are:

(a) Three carbon system.

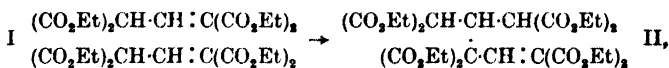
(b) Keto-cyclol system.

(c) Keto-lactol system.

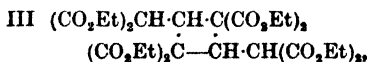


The last type is important as it includes the passage of acyclic sugars into the cyclic forms (pyranoses) (Chap. LVI, A1).

An example of (a) is met with in the condensation product II of ethyl  $\Delta^1$ -propene-1:1:3:3-tetracarboxylate I under the influence of piperidine (*Michael* reaction),

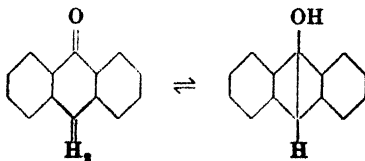


this product passes over into the *cyclobutane* ester III,

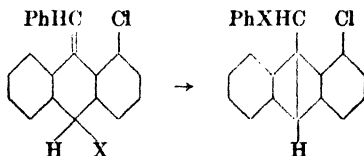


so that the equilibrium mixture contains 80 per cent of III and 20 per cent of II.

An example of ring-chain tautomerism is met with in anthracene derivatives, e.g. the interconversion of anthrone into anthranol (cf. Chap. XXXII, A.).



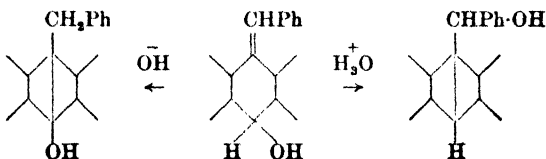
A number of dihydroanthracene derivatives have been examined by *Barnett* and others (B., 1927, 2353) and *Cook* (J. C. S., 1928, 2798),



where  $X = OH, OMe, OAc$ .

In these compounds there is a great tendency to pass over into the bridged ring state.

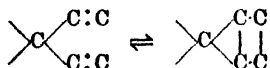
When  $X = OH$ , both cationotropic and anionotropic tautomerism occurs, the former by alkalis ( $OH^-$ ) and the latter by strong acids ( $H_3O^+$ ).



## 5. VALENCY TAUTOMERISM

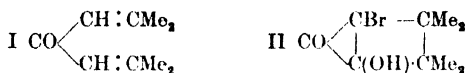
In all these cases there is no wandering of a hydrogen or other atom, but merely a redistribution of the valencies. There are two types: (a) Ring-chain; (b) Intra-annular.

(a) *Ring-chain*.—The one form is acyclic with two olefine links and the other a bicyclic compound,

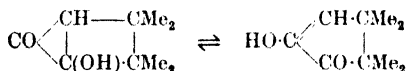


The best examples are met with in the phorone (p. 161) group. Phorone itself has the unsaturated structure I as shown by its bright red colour, its normal parachor value (Chap. LXXI, H2), its formation of a tetrabromide, its reduction to di-*iso*-butyl ketone, and its oxidation to acetone, oxalic acid and carbonic anhydride. On the other hand, the dibromo- and the hydroxy-

derivatives of phorone have the cyclic structure, e.g. the bromohydroxy compound II,

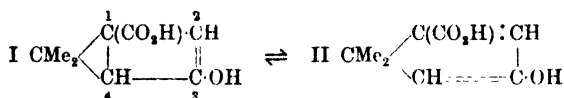


With some of the hydroxy compounds another type of tautomerism comes into play, viz. that between the dicyclic hydroxy- and the monocyclic keto-form:



(For methods of deciding structure cf. *Ingold* and *Schoppe*, J. C. S., 1928, 365.)

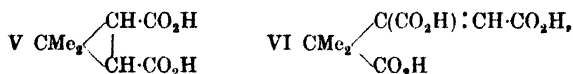
(b) *Intra-annular*.—Both forms are cyclic, the one form has an unsaturated monocyclic structure and the other a dicyclic structure. An example which has been closely studied is that of the monobasic acid I, which can react in the tautomeric form II (*Farmer, Ingold and Thorpe*, J. C. S., 1922, 128).



As enolic compounds these are in equilibrium with the corresponding ketones, viz. I with III and II with IV,



so that the acid can exist as a mixture of all four forms. The products of oxidation with ferricyanide, viz. caronic acid V and dimethylaconitic acid VI,



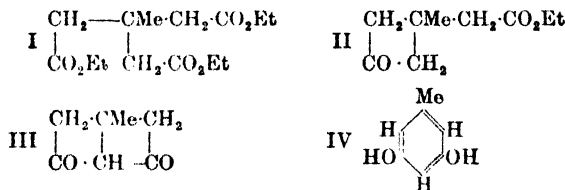
indicate structures I or III and II or IV. The formation of an isonitroso compound indicates the presence of the  $\text{CH}_2\text{-CO}$  group, and the isonitroso compound on hydrolysis yields a diketonic acid which on oxidation with  $\text{H}_2\text{O}_2$  yields dimethylaconitic

acid and hence has the structure  $\text{CMe}_2 \begin{matrix} \diagup \text{C}(\text{CO}_2\text{H})\text{:CH} \\ \diagdown \text{CO} \text{---} \text{CO} \end{matrix}$ . The stable form of the original monobasic acid thus appears to have the unsaturated ketonic structure IV.

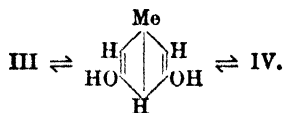
When the corresponding 1:2-carboxylic and 1:2:4-tricarboxylic acids are examined, the stable form appears to be the enolic as it gives a yellow colour with ferric chloride, forms no isonitroso compound, its ester is readily alkylated, and on oxidation it yields much caronic acid. The dibasic acid appears to be a mixture of two enolic forms corresponding with I and II, and the tribasic acid mainly type I.

The stability of the bicyclic type is largely due to the presence of the gem dimethyl group, and if these are replaced by hydrogen or even by the cyclohexyl group, the stable types are II and IV.

*Ingold* has studied similar phenomena in six-membered carbon rings. The action of sodium on ethyl ethane-*aaa*-triacetate acid I by the elimination of ethyl carbonate gives the cyclic butanone ester II, and this by elimination of EtOH gives the bicyclic compound III.



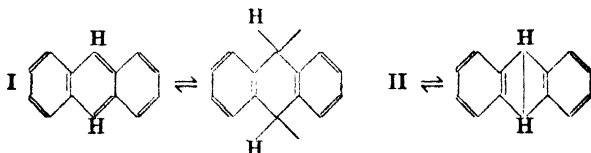
The product actually isolated is orcinol IV, which can be regarded as formed from III by keto enolic followed by intra-annular tautomerism:



Isophorone,  $\text{CMe}_2 \begin{matrix} \diagup \text{CH}_2\text{---CO} \\ \diagdown \text{CH}_2\text{---CMe} \end{matrix} \text{CH}$ , is another example in

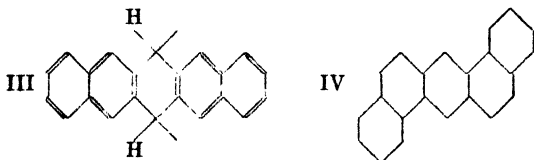
which three types of isomerism are involved: (a) The 3 carbon  $\alpha\beta$ ,  $\beta\gamma$  type; (b) the keto enolic; (c) intra-annular.

**Trans annular valency tautomerism.** *Clar and John* (B., 1932, 503) depict anthracene as tautomeric in the sense that the *o*-quinonoid form I can pass into the diradical form (R) II, where the meso carbon atoms are represented with free bonds or as tervalent:



This would account for the reactivity of the meso-positions. The R form is comparable with triphenylmethyl, and it is found that 9:10-diarylanthracenes, although colourless, give yellow solutions, and the intensity of the colour deepens with rise of temperature.

Similar tautomerism can occur with 2:3:6:7-dibenzanthracene III, which is coloured and remarkably reactive, whereas with the isomeric 1:2:5:6-dibenzanthracene the



benzenoid structure appears to be the stable one as it is colourless, yields colourless solutions, and is not so reactive.

## LIV. ISOTOPES OF HYDROGEN AND OXYGEN: DEUTERIUM COMPOUNDS

### A. Heavy Hydrogen

The recognition of an isotope of hydrogen with an atomic weight of 2 and the isolation of heavy water  $D_2O$  from ordinary water have led to the preparation of typical carbon compounds in which hydrogen is more or less completely replaced by deuterium, e.g.  $CD_4$ ,  $C_2D_2$ ,  $CH_3 \cdot CO_2D$ ,  $C_6H_5D_3$ ,  $C_6D_6$ , &c.

It is obvious that the number of such compounds is enormous, as in many cases where several hydrogen atoms are present these can be replaced atom by atom.

It may be stated in general terms that the deuterium compounds closely resemble the corresponding hydrogen compounds in chemical properties just as  $D_2O$  closely resembles water, and even in physical properties there is remarkable similarity, the deuterium compound frequently having a boiling-point or a melting-point differing by only a few degrees from that of its hydrogen analogue.

The following are a few typical deuterium compounds:

**Deuteromethane**,  $CD_4$ , can be prepared from heavy water and aluminium carbide,  $Al_4C_3$ .

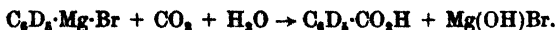
**Deuteroacetylene**,  $C_2D_2$ , from calcium carbide and 93 per cent heavy water.

**Deuterium cyanide**, from deuterium chloride and potassium cyanide, has a b.-pt.  $10^\circ$  and a m.-pt.  $2^\circ$  higher than hydrogen cyanide.

**Hexadeuterobenzene** is formed from benzene and heavy water on a nickel Kieselguhr catalyst at  $200^\circ$ , the operation being repeated four times. It is also formed by polymerization of  $C_2D_2$  with a tellurium catalyst, also by the action of  $DCl$  on benzene in the presence of aluminium chloride or by the action of heavy sulphuric acid on benzene when there is a progressive migration of deuterium into the nucleus. It has m.-pt.  $6.8^\circ$  compared with benzene  $5.5^\circ$ , and b.-pt.  $79.3^\circ$  compared with benzene  $80.12^\circ$ . It has, however, a smaller refractive index but a higher specific gravity.

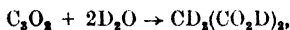
**Acetic deutero acid**,  $CH_3 \cdot CO_2D$ , from silver acetate and  $DCl$ , has m.-pt.  $13.3^\circ$ , a conductivity  $10^5K = 0.59$  (cf. acetic acid 1.34), and there is no tendency for the  $D$  atom to replace any of the hydrogens of the methyl group.

**Pentadeuterophenylcarboxylic acid**,  $C_6D_5 \cdot CO_2H$ , by the action of carbon dioxide on pentadeuterophenyl magnesium bromide and subsequent acidification:



It has m.-pt.  $120.9^\circ$  and at  $18^\circ$  is slightly more soluble in water than benzoic acid. Its molecular heat of combustion is 761380 kilo cal. as compared with 771400 for benzoic acid. The dissociation constants of the two acids are practically the same.

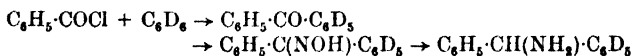
**Dideuteromalonic deuterio acid**,  $\text{CD}_2(\text{CO}_2\text{D})_2$ , from carbon suboxide and heavy water,



has a b.-pt.  $6^\circ$  lower than that of malonic acid, and when heated at  $140^\circ$ – $150^\circ$  loses carbon dioxide and yields trideuteroacetic deuterio acid,  $\text{CD}_3\cdot\text{CO}_2\text{D}$ , with m.-pt.  $15.75^\circ$  (acetic  $16.6^\circ$ ).

**Octadeuteronaphthalene**,  $\text{C}_{10}\text{D}_8$ , obtained as a by-product in the polymerization of deuterioacetylene, has m.-pt.  $77.5^\circ$  compared with naphthalene  $80^\circ$ . Other products formed are decadeuterofluorene and decadeuteropyrene (*Clemo and Robson*, J. C. S., 1939, 429).

**Pentadeuterophenylbenzylamine**,  $\text{C}_6\text{D}_5\cdot\text{CH}(\text{NH}_2)\text{C}_6\text{H}_5$ , is formed by the following series of reactions:



(*Clemo and McQuillen*, J. C. S., 1936, 808).

Catalytic deuteration of hydrocarbons occurs when a hydrocarbon and deuterium are heated to a moderate temperature in presence of palladinized palladium. Ethylene, cyclohexane and *n*-hexane react readily, the half-time period for cyclohexane is 11 mins. at  $97^\circ$  and for *n*-hexane 3 mins. at  $124^\circ$  (*Trans. Far.*, 1937, 678, 827).

*Ingold* and others (J. C. S., 1936, 1613) have studied the deuteration of benzene and certain substituted benzenes, viz. anisole, dimethylaniline, phenol, and benzenesulphonic acid in the presence of reagents such as  $\text{H}_2\text{SO}_4$ ,  $\text{H}_2\text{SeO}_4$ ,  $\text{H}_3\text{O}^+$ ,  $\text{PhOH}$ ,  $\text{H}_2\text{O}$ ,  $\text{OH}^-$ , containing some 2 per cent of the corresponding deuterio-compound, and find that the order given above is that of decreasing deuteration efficiency, and that for the substituents the order is  $\bar{\text{O}} > \text{NMe}_2 > \text{OMe} > \text{H} > \text{SO}_3\text{H}$ .

They also find that methylcyclohexane is deuterized readily and cyclohexane itself very slowly. Using  $\text{DHSO}_4$ , the relative ease of deuteration is methylcyclohexane  $>$  *n*-hexane  $>$  *n*-heptane  $>$  cyclohexane.

**Optical Activity.**—Numerous experiments have been made to isolate optically active compounds of the type  $\text{CHDR}_1\text{R}_2$ , but with the exception of the resolution of pentadeutero-

phenylbenzylamine by means of the hydrogen tartrates (*Clemons and McQuillen*, loc. cit.) without success. The values for the two bases in this case are  $[\alpha]_D^{16} + 5.0^\circ$  and  $-5.7^\circ$ , but this resolution has been queried as the  $C_6D_6$  used was apparently not pure. No resolution has been observed with compounds like  $C_6D_5 \cdot CHPh \cdot CO_2H$  or 2-deuterocamphane, and by addition of four D atoms to active ethylethynylcarbinol,  $OH \cdot CHEt \cdot C \equiv CH$ , an inactive compound  $OH \cdot CHEt \cdot CD_2 \cdot CHD_2$  is obtained (*J. A. C. S.*, 1937, 1497). Also the same product is formed by the action of deuterium on ethyl fumarate and ethyl maleate, and the resulting succinate could not be resolved (cf. *Rep.*, 1936, 228). Heating mandelic acid in NaOD solution for 16 hours gives a fully racemized product, but mandelic acid crystallized from  $D_2O$  gives a product in which 2H are replaced by 2D but activity is retained.

Small changes in the rotary power of a compound are noticed when the solvent is changed from  $H_2O$  to  $D_2O$ ; thus methylisopropylbenzylphenylammonium nitrate has  $[\alpha]_D^{20} + 114.08^\circ$  in  $H_2O$  and  $+113.30^\circ$  in  $D_2O$  (*Erlenmeyer and Schenkel*, *Helv.*, 1936, 1381; 1938, 114).

*Young and Porter* (*J. A. C. S.*, 1937, 328, 1437) have observed very slight alterations in optical rotation when the H in an active compound is replaced by D, e.g. the values of  $[\alpha]_D$  for  $CH_3 \cdot CH(C_6H_{13}) \cdot OH$  and  $CH_3 \cdot CH(C_6H_{13})OD$  are  $+7.68^\circ$  and  $+7.55^\circ$ .

A comparison of the mutarotation of *d*-glucose in pure water and pure deuterium oxide give the ratio  $k_{D_2O}/k_{H_2O} = 0.328$  with 18 per cent solutions at  $20^\circ$ , and for more dilute solutions the value 0.317 and the value  $k_{DOH}$  is intermediate between  $k_{H_2O}$  and  $k_{D_2O}$ . In the inversion of cane sugar catalysed by acids and in many reactions of a similar type the ratio  $k_{D_2O}^+/k_{H_2O}^+$  is always greater than unity, and varies from 1.67–2.0 for inversion of sucrose and hydrolysis of ethyl acetate to 3.0 for the decomposition of ethyl diazoacetate by acids.

Deuterium oxide does not diminish the velocity of esterification of an acid by hydrogen chloride to the same extent as water does (p. 200).

**Deuterizing power of different reagents.**—The increasing power of the following agents is in the order given,  $D_2SO_4$ ,  $D_3O^+$ ,  $DOAc$ ,  $D_2O$ , i.e. the power increases with the proton- or deuterion-donating power of the reagent, and in the case of



benzene derivatives deuterization follows the familiar rules for orientation and velocity in aromatic substitution (J. C. S., 1936, 1637; Z. phys., 1936, B., 33, 23).

With resorcinol and  $D_2O$  both H atoms of the two OH groups are immediately replaced by D and a much slower replacement of two nuclear hydrogens follows and the reaction is much accelerated in 0.1 N alkali solution. With quinol there is rapid replacement of the hydroxylic hydrogens followed by slow replacement of 4 nuclear hydrogens. With aniline hydrochloride and  $D_2O$  at  $60^\circ$  the compound  $C_6H_2D_3 \cdot ND_3Cl$  is formed after 3 hours.

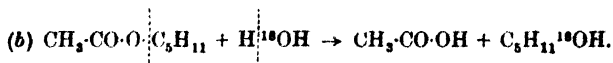
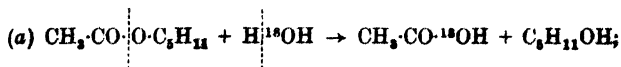
The use of deuterium compounds, e.g. a fat containing deuterium atoms, has proved of use in studying the fate of compounds in the animal organism.

### B. Heavy Oxygen

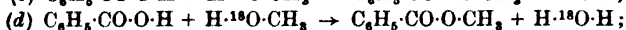
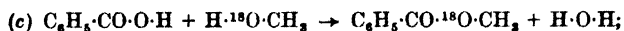
Compounds containing heavy oxygen,  $^{18}O$ , have been prepared. *Roberts* (J. Chem. Phys., 1938, 290; cf. Trans. Far., 1938, 432, 1219) examined the reactions between heavy oxygen water,  $H_2^{18}O$ , and numerous organic compounds. Methyl alcohol or nitrobenzene do not undergo any exchange in the presence of  $H_2^{18}O$  at  $25^\circ$  either with or without a catalyst, whereas acetic acid with 0.1 N hydrochloric acid as catalyst exchanges both oxygen atoms within 40 days and benzoic acid at  $100^\circ$ , either with or without a catalyst, exchanges its two oxygens in 4 hours. With trichloroacetic acid the exchange is complete after 42 hours at  $25^\circ$  and similarly with acetaldehyde after 24 hours, whereas there is no exchange with butyric acid or acetone after 24 hours at  $25^\circ$ , but partial exchange at  $100^\circ$ .

The use of heavy oxygen has proved of use in the study of the mechanism of certain reactions.

By the study of that between heavy water and amyl acetate in the presence of alkali, *Polanyi* and *Szabo* (Trans. Far., 1934, 508) were able to prove that the alcohol formed contains no heavy oxygen and hence the reaction proceeds according to (a) and not to (b):



Similarly, catalytic esterification is to be represented by (c) rather than (d):



as the water formed during the reaction between benzoic acid and methyl alcohol containing heavy oxygen is light water,  $\text{H}_2\text{O}$ , and contains no trace of  $\text{H}_2^{18}\text{O}$ . Care was taken to prove that under the conditions of the experiments neither methyl alcohol nor methyl benzoate exchanged with heavy water and benzoic acid extremely slowly (*Roberts and Urey, J. A. C. S., 1938, 2391*).

The use of phosphorus compounds containing radio-active phosphorus,  $^{32}\text{P}$ , has proved of value in tracing the stages in the formation of phosphorus complexes in the organism.

## LV. OILS AND FATS \*

These belong to the group of compounds termed **Lipoids**, or Lipids, which are characterized by: (1) Insolubility in water. (2) Solubility in ether, chloroform and benzene. (3) Their structures as esters of fatty acids. (4) Their utilization by living organisms. *Bloor* (1925) has classified them as follows:

### I. *Simple lipids.*

(a) Oils and Fats.

(b) Waxes, usually esters of higher fatty acids with higher monohydric alcohols.

II. *Compound lipids.* Esters containing other groups in addition to alcohol and fatty acid.

(a) Phospholipids (Phosphatides) containing phosphoric acid groups and nitrogen bases, e.g. lecithins and cephalins.

(b) Glycolipids. Compounds of fatty acids with a carbohydrate and containing nitrogen but no phosphoric acid, e.g. cerebositides.

III. *Derived lipids.*—Products formed from the above, e.g. fatty acids, sterols, higher monohydric alcohols.

\* *Chemie und Technologie der Fette und Fettprodukte*, H. Schönfeld; 2nd Edition, Wien, 1936-39; *Chemical Constitution of Natural Fats*, Hilditch, London, 1940; *Chem. Rev.*, 1941, 199.

## Oils and Fats

The oils and fats are esters of the trihydric alcohol, glycerol, and are natural products found in the vegetable and animal kingdoms. In the latter they form the fatty tissues of the body and are also present in fish, particularly in the liver; in plants they occur chiefly in spores, seeds, e.g. cotton, sunflower, linseed, and coats of fruit, e.g. palm and olive. They form the food reserves for the embryo during germination and early growth. During the early stages of germination the total fat undergoes little diminution, but then diminishes rapidly, and during this stage contains much free fatty acid and the iodine value is lower than that of the original oil. According to *Rhine* (1926) the fat is not transported as such, but is first converted into carbohydrate, and the view is held that it is formed in the cells from carbohydrates. In the early stages of development the seeds contain much free fatty acid, but this practically disappears as maturity is reached. It is to be noted that fats from the tropics contain relatively more glycerides of saturated acids than those from cooler climates, the latter containing large amounts of esters of unsaturated acids. Hence drying and semi-drying oils are usually obtained from seeds from temperate climates, and glycerides containing two or three olefine linkings are relatively more sensitive to climatic conditions than those containing only one; thus the farther north soya bean or flax seeds are grown the higher the iodine value of their oils.

Members of a particular botanical family are often characterized by fats in which particular acids predominate, e.g.:

Kernels of *Palmae* yield lauric acid.

Kernels of *Myristaceæ*, e.g. myrtle wax, yield myristic up to 60 per cent.

Seeds of *Cruciferae*, e.g. mustard, rape, yield erucic up to 50 per cent.

Seeds of *Umbelliferae* e.g. parsley, celery, parsnip, yield petroselinic up to 75 per cent.

Seeds of *Chaulmoogra*, yielding chaulmoogric acid (cf. table).

Animals obtain only a small amount of their fats from plants; they synthesize them in the body probably from carbohydrates.

The fats are important from two view-points:

1. **The industrial.** They constitute food material for man, e.g. butter, ground nut oil and hardened oils, and are also used for the manufacture of soaps, candles, paints, varnishes, &c. (for saponification cf. C. and I., 1939, 87).

The scarcity of oils in Germany has led that country to manufacture fatty acids for soap and candle manufacture by the catalytic oxidation of high hydrocarbons from petroleum, but the purification is difficult.

2. Animal and plant metabolism (cf. Chap. LXIX, E.).

## A. Extraction and Refining

Two general methods of extraction are adopted: (1) Crushing between rollers and then pressing either hot or cold or a combination of both in hydraulic presses. A certain amount of oil is retained in the pressed cake which can be used for either feeding or manurial purposes. (2) Solvent extraction by means of light petroleum, carbon disulphide, carbon tetrachloride or di- and tri-chloroethylene (p. 855) in continuous extractors. By this method more oil can be extracted, but some solvents are inflammable and others toxic so that great care is required.

The process of refining is to remove colour, odour, colloidal matter and free fatty acid. One of the commonest methods is by means of Fullers' Earth activated by treatment with mineral acid and subsequent washing.

Many oils develop an objectionable odour and taste on standing due in some cases to oxygen, and in others to enzyme action. This is termed **rancidity**, and is accelerated by heat, light and certain metals. The products consist of mixtures of

aldehydes, among these epihydrinaldehyde,  $\begin{array}{c} \text{CH}_2 \\ \diagup \quad \diagdown \\ \text{O} \quad | \\ \diagdown \quad \diagup \\ \text{CH-CHO} \end{array}$ ,

ketones, lactones, hydroxy acids and acids of lower molecular weight. It is probably first started by autoxidation at an olefine linkage and the formation of a peroxide. The iodine value decreases and the acid value increases during rancidity.

## B. Industrial Examination of Fats and Oils

In order to ascertain the purity of any sample of fat or oil and to ascertain whether it is mixed with other oils or with non-fat adulterants, a number of physical and chemical tests are usually made. These include determination of (a) Specific gravity; (b) Refractive index; (c) Acid value (i.e. the number of mg. KOH required to neutralize the free acids in 1 gm. of oil); (d) Saponification value (the number of mg. KOH required to neutralize free acids and to hydrolyse glycerides in 1 gm. of fat); (e) Ester value difference between c and d; (f) Iodine value or number of grams of iodine absorbed by 100 gm. of fat. This is not measured directly, but in terms of ICl or Br<sub>2</sub> taken up by 1 gm. of fat. As there are no  $\alpha\beta$ -unsaturated acids in combination with glycerol, and as there are very few conjugated double bonds, this gives a very good measure of the unsaturated nature of the acyl groups present, as each double bond uses up one mol. of ICl or Br<sub>2</sub>. Non-drying oils have values below 100, semi-drying values 100-130, and drying oils values above 130. (g) Thiocyanogen or rhodan value (*Kaufmann*, 1925), i.e. number of grams of thiocyanogen (SCN)<sub>2</sub> absorbed by 1 gm. of fat. With this reagent an acid with one double bond becomes fully saturated, whereas in an acid with two double bonds (linolic) only one of them reacts, so that in a mixture of oleic and linolic acids the proportions of the two can be calculated from the difference between the iodine and thiocyanogen values. (h) Acetyl value by treatment with Ac<sub>2</sub>O to determine the presence of free OH groups as in castor oil.

## C. Chemical Composition

Since *Chevreul* first proved that the fats are glycerides of normal saturated and unsaturated acids, e.g. palmitic, oleic and stearic, it has been assumed that the main components are **simple** glycerides, i.e. tripalmitin, tristearin and triolein, and that the consistency of any fat depends upon the relative proportions of these components. In 1897 the fat from the seeds of the tropical plant, *Allanblackia*, was found to consist mainly of the **mixed** glyceride, **oleodistearin**, C<sub>3</sub>H<sub>5</sub>(O·CO·C<sub>17</sub>H<sub>35</sub>)<sub>2</sub>(O·CO·C<sub>17</sub>H<sub>33</sub>). This compound was actually

isolated, and it is now generally conceded that mixed glycerides are the rule and not the exception in natural fats and oils; simple glycerides are formed when one particular acid is present in such large amounts that all of it cannot be utilized in forming mixed compounds. In seed fats the saturated and unsaturated acids form mixed glycerides in the proportion of roughly 1.5 saturated to 1.0 unsaturated acyl groups. If there is a surplus of saturated acyl above this ratio then fully saturated glycerides are formed, i.e. when the saturated acids comprise more than 60 per cent of the total fatty acids; similarly it is highly improbable that fully unsaturated glycerides are present unless the unsaturated acids form more than 40 per cent of the total acids. An exception appears to be laurel seed oil, as, although about 50 per cent of the total acid is unsaturated, the whole of the lauric acid is present as trilaurin. These generalizations do not hold in the case of animal fats or oils from the pericarp.

Mixed glycerides can often be isolated by careful fractional crystallization at low temperatures, or they may be completely hydrogenated and the chief products, e.g. tristearin,  $\alpha$ -palmito- $\alpha'$ - $\beta$ -distearin (m.-pt. 63.5°), and  $\beta$ -palmito- $\alpha\alpha'$ -distearin formed from cacao butter, separated (J. S. C. I., 1933, 237T; 1936, 95T), and in this particular case an almost complete analysis of the glycerides present has been worked out.

Useful information can also be obtained by investigating the saturated glycerides formed during progressive hydrogenation (*Hilditch and Stainsby*, Bio. J., 1935, 90, 559; cf. also J. S. C. I., 1935, 336T). Thus pig depot fat contains 80 per cent of  $\beta$ -monopalmito-glycerides and about 50 per cent of steardioleins.

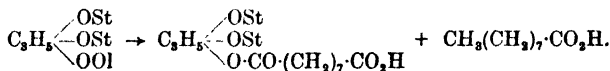
Typical composition of fats (J. S. C. I., 1938, 448T):

						Borneo Tallow*	Cacao Butter†
Oleodistearin	..	..	..	..	..	40	19
Oleopalmitostearin	..	..	..	..	..	31	52
Steardiolein	..	..	..	..	..	13	12
Palmitodiolein	..	..	..	..	..	3	9
Oleodipalmitin	..	..	..	..	..	8	6
Fully saturated, mainly palmitostearins	..	..	..	..	..	5	2

By carefully controlled oxidation of fats the unsaturated acyl groups can be oxidized while still attached to glyceryl,

\* Seed fat of *Shorea stenoptera*.      † Seed fat of *Theobroma cacao*.

whereas any saturated acyl remains intact (*Hilditch*, J. C. S., 1927, 3106; J. S. C. I., 1928, 261T). Thus a completely saturated glyceride is not oxidized, whereas one containing 1, 2 or 3 unsaturated acyl groups will give glycerides with acidic properties which can readily be separated from the neutral fully saturated compounds, e.g.:



A number of mixed glycerides have been prepared by *King* and others, and their physical constants determined (J. A. C. S., 1930, 365; 1932, 705; 1934, 1191, 1724). *Fairbourne* (J. C. S., 1930, 369) gives methods for preparing  $\alpha$ -,  $\beta$ -, mono-,  $\alpha\beta$ -,  $\alpha\alpha$ -, di-, and  $\alpha\alpha\beta$ -triglycerides.

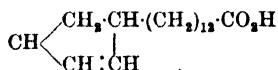
#### D. Compounds from Fats and Oils

The fat may be distilled by the process of molecular distillation (J. S. C. I., 1939, 49T); free fatty acids pass over first at 120°–150°, then the glycerides at 220°–260°, and the residue contains proteins, phosphatides, &c.

1. **Non-glycerides.** Quite a number of compounds other than glycerides are present in oils and fats: (a) Phytosterols (Chap. LXII, A.); (b) phosphatides; (c) vitamins (Chap. LXVIII, A.); (d) ketones. Diacetyl (Chap. IX, F.) is the odoriferous principle of butter and tends to facilitate rancidity. Completely washed butter keeps better, and the addition of a trace of maleic acid tends to prevent rancidity; methyl nonyl and methyl heptyl ketones are present in cocoa-nut oil and probably due to rancidity. (e) Alcohols and hydrocarbons. The unsaturated hydrocarbon squalene (Chap. LVII, G.) occurs in certain fish oils and olive oils, and the hydrocarbon **pristane**,  $\text{C}_{18}\text{H}_{38}$ , in liver oils and fish oils, and the alcohol ethers batyl and selachyl alcohols (p. 233) probably as glycerides.

2. **Saturated acids.** The saturated and also unsaturated acids obtained by hydrolysing fats are, with a few exceptions, normal acids containing an even number of carbon atoms and ranging from butyric ( $\text{C}_4$ ) to melissic ( $\text{C}_{30}$ ). The exceptions are isovaleric acid,  $\text{CMe}_2\text{-CH}_2\text{-CO}_2\text{H}$ , present in the head and blubber oils of the dolphin and porpoise, and chaulmoogric

acid, present in species of *chaulmoogra* and *hydnocarpus*; it has been synthesized by *Perkins* and *Cruz* (J. A. C. S., 1927, 1070) and has a cyclopentene structure:



**3. Unsaturated acids.** Only one hydroxy unsaturated acid is known, viz. ricinoleic acid from castor seed oil, and only one with a triple bond, viz. Tariric acid.

The unsaturated acids range from  $\text{C}_{10}$  to  $\text{C}_{24}$ , but the commonest are the  $\text{C}_{18}$ . The  $\text{C}_{16}$  acids occur in butter (3–4 per cent) and pig's fat, and also in many vegetable oils (under 1 per cent), and vary as to degree of unsaturation. The majority contain 1 olefine link. Several linolic acids with two olefine links and several linolenic acids with three olefine links are known. No acid contains an  $\alpha\beta$ -olefine link, and where two or more such links are present they are not conjugate with the exception of elaeostearic acid isomeric with the linolenic acids. These points are of importance as the determination of the iodine value of an oil would not be possible if  $\alpha\beta$ -unsaturated or conjugated olefine acids were common.

For percentage composition of acids from oils cf. Thorpe's Dict. Supp., Vol. II.

## OILS AND FATS

### Individual unsaturated acids:

I: Decenoic, $\text{C}_{10}\text{H}_{18}\text{O}_2$	$\text{CH}_2 : \text{CH}(\text{CH}_2)_7 \cdot \text{CO}_2\text{H}.$
Myristoleic, $\text{C}_{14}\text{H}_{26}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_7 \cdot \text{CH} : \text{CH}(\text{CH}_2)_5 \cdot \text{CO}_2\text{H}$ or $\text{CH}_3(\text{CH}_2)_3 \text{CH} : \text{CH}(\text{CH}_2)_7 \cdot \text{CO}_2\text{H}.$
Palmitoleic, $\Delta^9$ -hexadecenoic acid,* $\text{C}_{16}\text{H}_{30}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_5 \text{CH} : \text{CH}(\text{CH}_2)_7 \cdot \text{CO}_2\text{H}.$
Oleic, $\Delta^9$ -octadecenoic acid, $\text{C}_{18}\text{H}_{34}\text{O}_2$	$\text{CH}_3 : [\text{CH}_2]_7 \text{CH} : \text{CH}(\text{CH}_2)_7 \cdot \text{CO}_2\text{H} \text{ (cis).}$
Petroselinic, $\text{C}_{18}\text{H}_{34}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_{11} \text{CH} : \text{CH}(\text{CH}_2)_4 \cdot \text{CO}_2\text{H} \text{ (cis).}$
Vaccenic, $\text{C}_{18}\text{H}_{34}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_6 \cdot \text{CH} : \text{CH}(\text{CH}_2)_6 \cdot \text{CO}_2\text{H}$ (trans).
Ricinoleic, $\text{C}_{18}\text{H}_{34}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_5 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_2 : \text{CH}(\text{CH}_2)_7 \cdot \text{CO}_2\text{H}.$
Gadoleic, $\text{C}_{20}\text{H}_{38}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_9 \cdot \text{CH} : \text{CH}(\text{CH}_2)_7 \cdot \text{CO}_2\text{H}$ or $\text{CH}_3[\text{CH}_2]_7 \cdot \text{CH} : \text{CH}(\text{CH}_2)_9 \cdot \text{CO}_2\text{H}.$
Erucic, $\text{C}_{22}\text{H}_{42}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_7 \cdot \text{CH} : \text{CH}(\text{CH}_2)_{11} \cdot \text{CO}_2\text{H} \text{ (cis).}$
Cetoleic, $\text{C}_{22}\text{H}_{42}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_9 \text{CH} : \text{CH}(\text{CH}_2)_9 \cdot \text{CO}_2\text{H}.$
Selacholeic or Nervonic $\text{C}_{24}\text{H}_{46}\text{O}_2$	$\text{CH}_3[\text{CH}_2]_7 \cdot \text{CH} : \text{CH}(\text{CH}_2)_{13} \cdot \text{CO}_2\text{H}.$

\* In numbering the C atom of the  $\text{CO}_2\text{H}$  group is No. 1.



1: Tariric, $C_{18}H_{32}O_2$	$CH_3[CH_2]_{10}C[CH_2]_4CO_2H.$
2: Linoleic, $C_{18}H_{32}O_2$	$CH_3[CH_2]_4CH:CH-CH_2-CH:CH$ $[CH_2]_7CO_2H.$
3: Linolenic, $C_{18}H_{30}O_2$	$CH_3-CH_2-CH:CH-CH_2-CH:CH-CH_2-$ $CH:CH[CH_2]_7CO_2H.$
Elaeostearic, $C_{18}H_{30}O_2$	$CH_3[CH_2]_3CH:CH-CH:CH-CH:CH$ $[CH_2]_7CO_2H.$
Linolenic (œnothera), $C_{18}H_{30}O_2$	$CH_3-[CH_2]_4CH:CH-CH_2-CH:CH-CH_2-$ $CH:CH[CH_2]_4CO_2H.$
Conj. linolenic, $C_{18}H_{30}O_2$	$CH_3-CH_2-CH:CH-CH:CH:CH-CH:$ $CH-CH:CH-[CH_2]_7CO_2H.$
Chaulmoogric	$CH_2 \begin{cases} \diagup CH_2-CH-(CH_2)_{11}-CO_2H. \\ \diagdown CH:CH \end{cases}$

From the table it will be noticed that the groups  $\cdot CH[CH_2]_7\cdot CH:$  and  $\cdot CH[CH_2]_4\cdot CH:$  are very common.

The acids with one olefine link can exist in *cis* and *trans* forms, and X-ray and parachor measurements indicate that oleic, erucic and petroselinic acids are the *cis* forms and the isomerides formed by the action of nitrous acid are the *trans* forms. Vaccenic acid, on the other hand, is the *trans* form.

The acids with two olefine links can exist in *cis-cis*, *cis-trans*, *trans-cis* and *trans-trans* forms.

**Elaeostearic acid**,  $C_{18}H_{30}O_2$ , forms about 90 per cent of tung oil acids, and 67 per cent of oil from *Aleurites trisperma*; it was shown in 1929 to be capable of taking up 6 atoms of hydrogen in stages, the intermediate compounds being  $\Delta^9$ ,<sup>12</sup> diene acid and  $\Delta^{11}$  oleic acid, and hence contains the conjugate system  $CH_3\cdot[CH_2]_3\cdot[CH:CH]_3\cdot[CH_2]_7\cdot CO_2H$ . A structure confirmed by its high molecular refraction and by the products of ozonolysis, viz. valeric and azelaic acids formed from the end portions of the molecule. The system of conjugate bonds accounts for the low iodine value, as by the ordinary methods of determination it requires 6 days for complete addition.

**$\alpha$ -Licanic acid**,  $C_{18}H_{28}O_3$ , m.-pt. 74°-75°, obtained from the seed fat of *Licania rigida*, is the first ketonic unsaturated acid to be isolated from natural fats. It is a  $\gamma$ -keto-elaeostearic acid and on hydrogenation yields  $\gamma$ -ketostearic acid. Its structure is 4-keto- $\Delta^9$ ,<sup>11,13</sup>-octadecatrienoic acid (*Brown and Farmer, J. C. S., 1935, 1632*).

A conjugate tetrene acid,  $C_{18}H_{30}O_2$ , has been isolated from the seed fat of *Parinarium laurinum* (*ibid.* 759).

The different highly unsaturated acids of fish oils can be

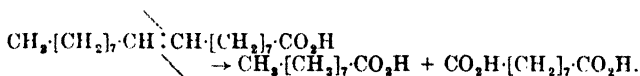
separated by the molecular distillation of their methyl esters (*Farmer and Van den Heuvel*, J. S. C. I., 1938, 24).

Minute amounts of  $\Delta^9$ -decanoic acid and a tetradecenoic acid,  $C_{14}H_{26}O_2$ , are present in butter fat and  $\Delta^{11}$ -octadecenoic acid, also in butter fat and in beef tallow (1 per cent).

Other unsaturated acids containing up to  $C_{24}$  and with one to five olefine linkings occur in salt-water fish oils.

**4. Separation of fatty acids from fats and oils.\*** If the percentage of unsaturated acids is high it is usual to separate the saturated and unsaturated acids by *Twitchell's* lead alcohol method and to convert separately into methyl esters by the *Fischer* method. By careful fractionation at 3–5 mm. pressure, using a *Pfeiffer* oil pump, and from *Ladenburg* flasks with two bulbs fitted with *Raschig* rings, and at a rate of 20 small drops per minute, it is found that alternate fractions are pure individual esters and the intermediate fractions are mixtures of two esters only. By this method it is possible not only to isolate the individual acids as methyl esters but also to determine the amount of each.

**5. Structure of unsaturated acids.** The method of ozonolysis has already been described (Chap. XLVIII, G.). *Armstrong and Hilditch* (J. S. C. I., 1925, 43T, 180T) use the methyl or ethyl esters of the acids and oxidize with powdered permanganate in hot acetone or acetic acid solution. The products often obtained in 80 per cent yields are a monobasic acid and the acid ester of a dibasic acid formed by the cleavage of the original molecule at the double bond. The product is then hydrolysed and the mixture of monobasic and dibasic acids separated by extraction with boiling light petroleum. With ordinary oleic acid the products are nononic and azelaic acids:



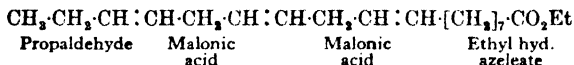
Using this method the following conclusions have been drawn. The myristoleic acid present in whale oil (1.0–1.5 per cent) is mainly the  $\Delta^9$ -compound with perhaps a little  $\Delta^8$ -acid. Palmitoleic acid is  $\Delta^9$ -hexadecenoic acid.

*Haworth* (J. C. S., 1929, 4190), using this method with linoleic acid from the soya bean and also from poppy seeds, obtained 80 per cent yields of *n*-hexoic, azelaic and oxalic acid, together

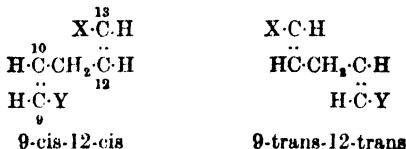
with a little malonic indicating the structure  $\Delta^{9,12}$ -octadecadienoic acid.

*Hilditch and Vidyarthi* (P. R. S., 1929, **122**, 563) recommend the following method for determining the positions of double bonds in the polyene acids. The methyl ester is partially hydrogenated until it consists of monoethenoid compounds only, and is then oxidized by the above permanganate method and the mixture of mono- and dibasic acids examined. Partially reduced methyl linoleate treated in this way gives *n*-hexoic, azelaic and oxalic acids.

The structure of the linolenic acid obtained by the removal of bromine from the solid hexabromide (m.-pt. 181°) based on the ozonolysis of its ethyl ester to propaldehyde, malonic acid and ethyl hydrogen azelaate is that of  $\Delta^{9,12,15}$ -octadecatrienoic acid:



*Suzuki* (P. Roy. Acad., Tokyo, 1931, 15) has attempted to elucidate the configurations of certain linoleic acid ( $\Delta^{9,12}$ -diene acids). The acid from most seeds, e.g. linseed, cotton seed, soya bean) yields both a solid tetrabromide (m.-pt. 114°) and a liquid isomeride. By the action of alcoholic potash on the two tetrabromides at 0°–20° and by a comparison of the products with those obtained by the action of the same reagent on oleic acid dibromide and eleadic acid dibromide, the conclusion is drawn that the acid yielding the tetrabromide melting at 114° is the 9-*cis*-12-*cis* acid and the one yielding the oily tetrabromide the 9-*trans*-12-*trans* acid:



where X = CH<sub>3</sub>·[CH<sub>2</sub>]<sub>4</sub>· and Y = ·[CH<sub>2</sub>]<sub>7</sub>·CO<sub>2</sub>H.

On the other hand, the linoleic acid derived from *Seiden-raupen* oil gives a tetrabromide melting at 60°, and is probably the 9-*trans*-12-*cis* acid.

**Oleic acids.**—By the partial hydrogenation of ordinary oleic esters (i.e.  $\Delta^9$ -compound) a certain amount of isomers

are formed, viz. elaidic acid (the *trans* isomeride),  $\Delta^8$ - and  $\Delta^{10}$ -acids formed by a shifting of the double bond, and further by the partial hydrogenation of linoleic esters addition can take place at either the 9:10- or the 12:13-position, thus yielding the  $\Delta^{12}$ - and  $\Delta^9$ -oleic acids in either *cis* or *trans* or both forms. The oleic acid present in a partially hydrogenated oil is thus a complex mixture (P. R. S., 1928, B., 103, 111).

## E. Vegetable Fats and Oils

1. **In the fruit coat or pericarp surrounding the endosperm.** Examples, palm and olive oils and Chinese tallow. They vary from hard fats to oils of the "drying" type, but their chief constituents are glycerides of palmitic, oleic and linoleic acids. The composition of the oil from the fruit coat and of the oil from the seeds of the same plant often differ considerably. With the olive the composition of the two is much the same, but with *Stillingia* the former oil is a hard, relatively saturated fat, whereas the latter is a highly unsaturated oil. The simple glyceride, tripalmitin, is often present in fruit-coat fats even when the palmitic acid is only 10 per cent of the total acids, but otherwise the glycerides are of the mixed type wherever possible. Olive oil acid contains as much as 80 per cent of oleic acid, and hence the oil has as much as 50 per cent of triolein.

2. **Seed fats.** The acids present in seed fats can vary considerably, but usually members of the same botanical family display great similarity in the specific fatty acids. The common glycerides are those of palmitic, oleic, linolic and linolenic acids, i.e.  $C_{16}$  and  $C_{18}$  acids. Higher saturated acids, stearic and arachidic, and lower, myristic, are usually present to less than 3 per cent of the total acids. The seeds from shrubs, trees, conifers, many herbs and also from such families as *Rosaceæ*, *Compositæ*, *Labiataæ* and *Gramineæ* belong to this group, also the oils including the well-known drying and semi-drying oils, e.g. sunflower, safflower, sesame, linseed, hemp, poppy, &c. In many of these the percentage of saturated acid is under 10. The chief acids are the unsaturated of the  $C_{18}$  group, viz. oleic, linolic and linolenic, and the drying properties depend, to a large extent, on the proportions of the more unsaturated acids present as mixed unsaturated glycerides.

The kernel fats, e.g. cocoa-nut oil, nutmeg butter, palm kernel oil, dika butter, contain very little unsaturated acids and often consist of as much as 66–86 per cent of fully saturated glycerides. The saturated acids from the fats contain lower homologues of palmitic acid, viz. caprylic,  $C_8$ , 42–49 per cent; capric,  $C_{10}$ , lauric,  $C_{12}$ , 45 per cent; and myristic,  $C_{14}$ , 13–26 per cent.

The oils with appreciable amounts of stearic acid are obtained from certain tropical families, e.g. *Sterculaceæ*, viz. cacao butter with 35 per cent; *Guttiferæ*, e.g. *Allanblackia* of different species 60 per cent; and *Sapotaceæ*, e.g. *palaquium oblongifolium* 54 per cent. The higher saturated fatty acids, e.g. arachidic,  $C_{20}$ , and lignoceric,  $C_{24}$ , are met with in small quantities in many fats and in large quantities in the fats of members of *Sapindaceæ* and *Leguminosæ*.

## F. Land Fauna Fats

The major components of the fats of animals as distinct from fish are. palmitic, 25–30 per cent, oleic and linolic together about 70 per cent, and in some, mainly herbivorous, stearic acid is also an important constituent. Rodents and birds also yield about 7 per cent of palmitoleic acid,  $\Delta^9$ -hexadecenoic acid, and also small amounts of  $C_{20}$  and  $C_{22}$  unsaturated acids. Rodents and birds give fats containing 25–30 per cent of palmitic and only a little stearic acid and contain about 3 per cent of tripalmitin.

In the case of non-herbivorous animals the amount of saturated glycerides, mainly palmito-stearins, is much greater, and the even distribution of saturated and unsaturated acyl groups characteristic of seed fats does not apply. Thus a seed fat with 60 per cent of saturated acids contains very little completely saturated glyceride, whereas a tallow (animal fat) with 30 per cent of palmitic and 25 per cent of stearic acid in the mixed acids contains about 26 per cent of palmito-stearins (see table, Rep. Ind., 1935, 412).

In milk fats the acids are roughly palmitic 25 per cent, oleic 35–45 per cent, and a large proportion of butyric acid and other saturated acids of low molecular weight, and the proportion of saturated glycerides is relatively high. Composition of butter fat: glycerides of *n*-butyric 3–4, caproic 1.5–2,

caprylic 1, capric 2-3, lauric 3-4, myristic 7-20, palmitic 21-28, stearic 7-12, arachidic 1-1, oleic 30-40, linolic 2-4 per cent. These compositions apply to animals on normal diet and will vary with the diet, especially if much oil or fat is present, as the acids of the ingested fat are found in the body fat of the animal or even in the milk.

## G. Aquatic Fauna Fats

### 1. Marine

The oils from salt-water fish are highly unsaturated, and contain acids with 16, 18, 20, 22, 24 atoms of carbon and with as many as six olefine links and possibly an acetylene link. Much work has been done on the highly unsaturated acids in Japan by *Tsujimoto Toyama* and others, and in this country by *Lovern* and by *Farmer*.

The structures of very few of the acids can be regarded as established beyond question.

**Gadoleic acid** with the double link in position 9:10 (or position 11:12) occurs in cod-liver oil, Japanese sardine oil, herring oil, and certain blubber oils.

**$\Delta^9$ -Palmitoleic acid** is present in many fish oils, but is also met with in vegetable oils, e.g. lycopodium spores.

Other monoene acids present in fish oils are myristoleic acids, e.g.  $\Delta^4$ -tetradecenoic acid from tsuzu oil, the isomeric  $\Delta^5$ -acid from sperm-head oil, and the  $\Delta^9$ -acid present in ordinary whale oil.

Fats of *Teleostei* fish (liver oils of cod, flesh oils of herrings, and the blubber of large marine animals such as whales or seals) have the composition palmitic 15, palmitoleic 15-20,  $C_{18}$  acids 30,  $C_{20}$  20-25, and  $C_{22}$  10 per cent, the  $C_{20}$  and  $C_{22}$  acids containing as a rule 3 or 4 olefine bonds.

*Elasmobranch* fish, in the fat of which large amounts of squalene are found, contain monoene acids with  $C_{20}$  and  $C_{22}$  carbon atoms and about 10 per cent of selacholeic acid, i.e.  $\Delta^{15}$  tetracosenoic acid,  $C_{24}H_{46}O_2$ , which is identical with the nervonic acid of brain.

*Sperm oils* contain esters derived from oleyl, cetyl and other monohydric alcohols in place of glycerol and are liquid waxes and not fats.

## 2. Fresh Water

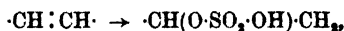
The oils from these differ in containing rather more palmitoleic acid, much more  $C_{18}$  acids and less  $C_{20}$  and  $C_{22}$  acids. Apparently frogs give an oil intermediate between that of an aquatic and a land animal.

Fats can be synthesized by growing moulds on carbohydrate media, also by the esterification of fatty acids with glycerol. For the latter purpose the acids recovered by removing the free fatty acids from oils and fats in the process of refining are used especially when these acids are removed by a continuous process of distillation under very low pressures. *Twitchell's* reagent is more effective as a synthesizing than a splitting agent.

## H. Modern Detergents and Boiled Oils

Important industrial products can be obtained by the action of sulphuric acid on certain oils or acids from oils. Turkey red oil is obtained by treating ricinoleic acid with concentrated sulphuric acid at low temperature and neutralizing with ammonia or caustic soda. It has good lathering properties, and is largely used in connexion with alizarin dyeing.

Sulphated products are also formed by the action of sulphuric acid on olefine acids or their glycerides. The  $SO_3(OH)_2$  adds on to the double bond,



and this neutralized gives a sodium salt with detergent properties.

The hydrogen sulphates of higher fatty alcohols,  $RO\cdot SO_3\cdot OH$ , in the form of their sodium salts are largely used as soap substitutes (Chem. Met. Eng., 1933, 249; C. and I., 1934, 24). The alcohols required can be obtained by reducing a fatty acid or even its glyceride by heating with hydrogen at  $200^\circ$  under 200 atm. pressure in the presence of a copper chromite catalyst. The important ones are those derived from lauryl, octadecyl and oleyl alcohols, and are known commercially as *Gardinols*.

Glycerides of the type  $OH\cdot C_3H_5\cdot (OX)\cdot O\cdot SO_3\cdot ONa$ , where X = stearyl or similar groups, can also be used for the same purpose.

## Boiled Oils

Another process of technical importance in the oil industry is the boiling of drying oils, as these products are of great value in the paint and varnish industry. When the drying oils are heated ("boiled") a polymerization of the glycerides derived from linolic and linolenic acids takes place. This has been proved, as when a boiled oil is transformed into the ethyl esters by alcoholysis and then subjected to distillation under very low pressures, all the saturated acids and oleic acid present pass over as ethyl esters, whereas the more unsaturated acids remain in the residue as polymerized ethyl esters (*Steger and van Loon, Rec. trav., 1935, 387, 428, 750*).

## Waxes

Other compounds present in oils are:

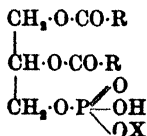
Oleyl alcohol,  $C_{18}H_{35}OH$ , present in sperm-whale oil.

Cetyl laurate and palmitate in spermaceti from the sperm-head oil.

Ether glycols of the type  $R \cdot O \cdot C_3H_5(OH)_2$ , where  $R = C_{16}H_{33}$ ,  $C_{18}H_{35}$ , and  $C_{18}H_{37}$  are present as fatty acid esters in shark and ray liver oils.

## I. Phosphatides

The structure of the phosphatides is represented in the following formula:



where  $\cdot COR$  represents higher fatty acyl groups, one saturated, e.g. palmitoyl or stearoyl, and the other unsaturated, e.g. oleyl or linoloyl, and  $X$  represents the choline group,  $\cdot O \cdot CH_2 \cdot CH_2 \cdot NMe_3OH$ , in the case of lecithins; and the choline group,  $\cdot O \cdot CH_2 \cdot CH_2 \cdot NMe_3$ , in the case of cephalins. They are both present in yolk of egg and nervous tissue, but



the former in larger quantities. Most of the isolated products are probably mixtures, and there are structural isomerides, viz.  $\alpha$  or  $\beta$  according to the substitution of an  $\alpha$ - or the  $\beta$ -H (of OH) in glycerol.

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## LVI. CARBOHYDRATES \*

### A. Monosaccharides

The spatial configurations of the monosaccharides as represented by aldose structures and as deduced by *Fischer* and others are given in Chap. XIV.

A simple method of denoting such configurations has been described by *Wohl* (B., 1922, 1404; 1923, 309), who suggests that instead of writing the full formula, attention is drawn to the H and OH groups on the right side of the molecule only; thus if the grouping with OH on right is termed + that with H on right is -. Thus *d*-glucose can be written: OH, OH, H, OH, or simply + + - +. On this basis the formulæ for the monosaccharides are given in the table below. These formulæ are for the *d*-compounds, and the *l*-compounds are the antipodes of these. The configuration for *d*-glucose is selected arbitrarily, but those of the other compounds are all based on this, e.g. *d*-xylose and *d*-gulose are the compounds, the configurations of which correspond with that of *d*-glucose whether they rotate to the right or left. In order to avoid ambiguity the letter *d* or *l* is used to denote the relationship to the parent substance—in the case of the saccharides—*d*-glucose, and the + or - after *d* or *l* indicates the actual sign of the rotation; thus ordinary fructose (lævulose) is written *d*(-)fructose, indicating that it has the same spatial relationships as *d*-glucose, but that its aqueous solution is lævo rotatory. The compounds termed *d*-gulose, *d*-idose, *d*-xylose and *d*-threose by *Fischer* are in reality related to *l*-glucose and are therefore written *l*(+) gulose, *l*(+) idose, &c.

\* *Carbohydrates*, E. F. and K. F. Armstrong, 1934.

Trioses	Tetroses	Pentoses	Hexoses
			$\left\{ \begin{array}{l} + + + + \\ d\text{-allose} \\ + + + - \\ d\text{-altrose} \\ + + - + \\ d\text{-glucose} \\ + + - - \\ d\text{-mannose} \\ + - + + \\ d\text{-gulose} \\ + - + - \\ d\text{-idose} \\ + - - + \\ d\text{-galactose} \\ + - - - \\ d\text{-talose} \end{array} \right.$
	$\left\{ \begin{array}{l} + + \\ d\text{-erythrose} \\ \\ + - \\ d\text{-threose} \end{array} \right.$	$\left\{ \begin{array}{l} + + + \\ d\text{-ribose} \\ + + - \\ d\text{-arabinose} \\ \\ + - + \\ d\text{-xylose} \\ + - - \\ d\text{-lyxose} \end{array} \right.$	
$d\text{-glycerose} +$			

The order given is that of proximity to the  $\text{CH}_2\text{OH}$  group.

*Wohl* has been able to prove that in glycerose the one asymmetric carbon has the same absolute configuration as carbon atom number 5 in *d*-glucose.

The fact that in the aldoses the aldehyde reactions are relatively suppressed led to other structures being assigned to glucose, e.g. the enol formula (1895)  $\text{OH}\cdot\text{CH}:\text{C}(\text{OH})\cdot$  in place of  $\text{O}:\text{CH}\cdot\text{CH}(\text{OH})\cdot$ , the aldehyde hydrate formula (*Fittig*) and various ring formulæ, e.g. ethylene oxide type (1870), butylene oxide type (*Tollens*, 1883), and finally the amylen oxide type by *Haworth* in 1926.

The butylene oxide structure was suggested by *Fischer* (B., 1893, 2400) for the two stereo-isomeric methylglucosides as they could not be represented by the acyclic formulæ and was subsequently extended to  $\alpha$ - and  $\beta$ -glucoses when *Armstrong* (J. C. S., 1903, 1305) was able to show that the  $\alpha$ -glucoside on hydrolysis with maltase gives nearly pure  $\alpha$ -glucose and the  $\beta$ -glucoside with emulsin gives nearly pure  $\beta$ -glucose, but a drop of dilute ammonia produces the stable equilibrium mixture of the  $\alpha$ - and  $\beta$ -glucoses.

The only reason for accepting the five-atom ring structure appears to have been the fact that lactones can be reduced by sodium amalgam and dilute acid to sugars, e.g. *d*-gluconolactone to *d*-glucose, and it was assumed that the five-membered ring remains intact. Different structural formulæ were suggested for the  $\alpha$ - and  $\beta$ -methylglucosides by *Nef* (A., 1914, 403, 204), e.g. an ethylene oxide formula for the  $\beta$ , but their



that in the formation of a ring from the open-chain formula a rotation of the link between C, No. 5, and C, No. 6, through  $120^\circ$  occurs.

The terms  $\alpha$  and  $\beta$ , as applied to the two stereo-isomeric sugars or their monomethyl derivatives, are apt to be confusing. Originally attempts were made to denote as  $\alpha$ -compounds all those derivatives in which the configuration of the C atom No. 1 was similar to that in  $\alpha$ -glucopyranose, but as *Walden* inversion frequently occurs the deduction made might be incorrect, and at present it is usual, in the case of a pair of isomerides, to term the one with the higher dextro rotation  $\alpha$  and the other  $\beta$  (*Hudson's rule*).

According to *Isball and Pigman* (J. org., 1937, 505), the more dextro rotatory of the pair is termed the  $\alpha$ , when in the projection formulæ the O ring is on the right, but when the ring is on the left the less lævo rotatory is termed the  $\beta$ .

The separation of an  $\alpha$ - and  $\beta$ -compound can sometimes be effected by means of a definite crystalline compound with calcium chloride, e.g. *d*-methylguloside from a mixture.

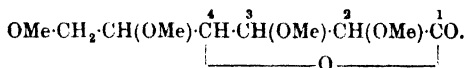
Mannose yields a crystalline derivative  $\text{ManCaCl}_2 \cdot 4\text{H}_2\text{O}$ , which is the mannofuranose form, and although very little of this is present in the original equilibrium mixture appreciable amounts can be isolated as the crystallization disturbs the equilibrium and more of the furanose compound is formed.

Rough approximations to the amounts of  $\alpha$ - and  $\beta$ -compounds present in an equilibrium mixture may be obtained by calculations from the initial rotation and the rotation at equilibrium, but the results are not accurate as small amounts of other products are also formed (probably  $\gamma$ -sugars) which affect the rotation.

All  $\beta$ -aldoses are oxidized by bromine more rapidly than the  $\alpha$ -compounds, the amounts of  $\alpha$  and  $\beta$  in an equilibrium mixture can be calculated from the rates of oxidation, and the values obtained are comparable with the amounts calculated from  $[\alpha]$ , assuming that only  $\alpha$ - and  $\beta$ -compounds are present.

## 1. PYRANOSE SERIES \*

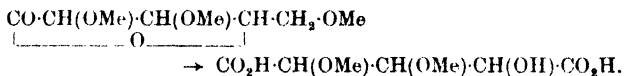
The arguments used by *Drew* and *Haworth* (J. C. S., 1926, 2303) for the pyranose structure are largely based on a study of the methylated sugar (cf. Chap. XIV, A.) and the corresponding acids and lactones. The argument that, since *d*-mannolactone on reduction yields *d*-mannose, the latter has the same five-membered ring as the former is of little value as it is quite possible that during the reduction the lactone ring may open and subsequently reclose in a different position, e.g.  $\gamma$ -lactone  $\rightarrow$  hydroxy acid  $\rightarrow$   $\delta$ -lactone. With a fully methylated lactone such a change is ruled out as, if the lactone forms the acid, the only type of lactone which can be formed is the same  $\gamma$ -lactone, as all other positions are occupied by OMe and not OH groups.



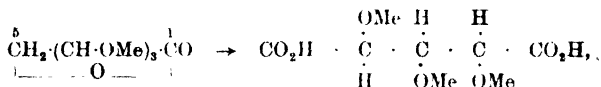
In 1914 *Nef* (compare also *Hedenberg*, J. A. C. S., 1915, 345) was able to obtain two isomeric lactones from *d*-gluconic acid. The ordinary or  $\gamma$ -lactone is readily obtained by heating the acid at 100° for a comparatively short time, and the isomeric  $\delta$ -lactone is formed when the acid or its ester is heated for a prolonged period at a lower temperature. Other monobasic acids derived from aldoses yield isomeric  $\gamma$ - and  $\delta$ -lactones, and, as a rule, the  $\delta$  form readily passes over into the more stable isomeride. A fully methylated lactone, either  $\gamma$  or  $\delta$ , is stable and cannot undergo isomerization. A polarimetric study of the rates of hydration of all the lactones and of their methylated derivatives, obtained by the methylation of the lactones or by the methylation of an aldose followed by oxidation, show that these lactones fall into two groups: (a)  $\gamma$ -lactones, which are only slowly hydrated, and (b)  $\delta$ -lactones, which are comparatively readily hydrated in aqueous solution, and thus the ease or difficulty with which any particular lactone undergoes hydration with consequent change of rotation can be utilized for ascertaining whether it belongs to the five-atom ring or the six-atom ring type. Oxidation experiments

\* *Constitution of Sugars*, Haworth, 1929.

with a typical  $\gamma$ - and a typical  $\delta$ -lactone have conclusively established the structure of the compounds. Thus the crystalline trimethylarabono- $\gamma$ -lactone, m.-pt.  $33^\circ$ , was characterized by its oxidation to 2:3-dimethoxy-4-hydroxyglutaric acid,  $\text{CO}_2\text{H}\cdot\text{CH}(\text{OMe})\cdot\text{CH}(\text{OMe})\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$ , and the formation of this compound was accompanied by the elimination of a methoxy residue at position 5 in the carbon chain,



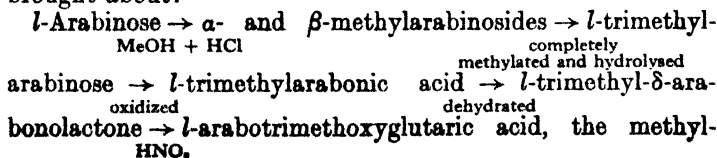
When the trimethyl-arabono- $\delta$ -lactone was oxidized in a similar manner with nitric acid it gave the optically active trimethoxyglutaric acid,



proving that the hydroxyl from which the lactone was derived cannot have been in position 4 ( $\gamma$ ) but in position 5 ( $\delta$ ).

One of the strongest arguments for the six-atom ring structure of the stable penta- and hexa-aldoes and ketoses is the oxidation of their methyl ethers to a 2:3:4-trimethoxyglutaric acid,  $\text{CO}_2\text{H}\cdot\text{CH}(\text{OMe})\cdot\text{CH}(\text{OMe})\cdot\text{CH}(\text{OMe})\cdot\text{CO}_2\text{H}$ . It is clear that such a compound must exist in a number of stereoisomeric forms, the actual number theoretically possible is six, and each sugar gives rise to a single isomeric form, which can be identified by conversion into its amide or methylamide,  $\text{NHMe}\cdot\text{CO}[\text{CH}(\text{OMe})]_3\cdot\text{CO}\cdot\text{NHMe}$ . These are all crystalline compounds with well-defined melting-points. The name given to a particular trimethoxyglutaric acid is usually derived from the pentose from which it can be obtained by oxidation, e.g. *d*-arabotrimethoxyglutaric acid, xylotrimethoxyglutaric acid.

***l*-Arabinose:** The following series of reactions are readily brought about:

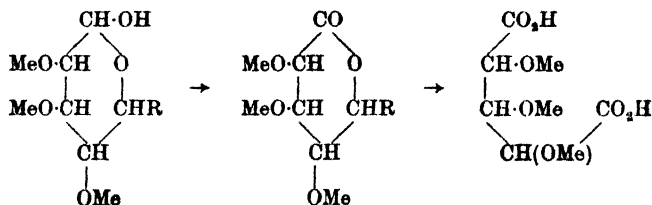


amide of which melts at  $172^{\circ}$ . The formation of a 2:3:4-trimethoxyglutaric acid is a clear proof that in the trimethyl-lactone, and hence also in the trimethylarabinose, the three methyl groups are in adjacent positions and not terminal positions 1 and 5. As the reducing group which is in position 1 always takes part in the oxide ring of the aldose molecule, it follows that this oxide formation occurs at the 1:5-positions, i.e. it is a six-atom ring.

**d-Glucose.**—When a similar series of reactions is carried out with *d*-glucose the respective products are:  $\alpha$ - and  $\beta$ -methylglucosides  $\rightarrow$  tetramethylglucose  $\rightarrow$  tetramethylgluconic acid  $\rightarrow$  tetramethyl- $\delta$ -gluconolactone  $\rightarrow$  xylotrimethoxyglutaric acid. The formation of this 2:3:4-trimethoxy acid shows definitely that the oxide ring cannot engage positions 3 or 4 in the methylated aldose chain as these must be methylated; hence it must involve either position 5 or 6 of the hexose chain. The latter alternative is excluded by the fact that a 2:3:4:5-tetramethylgluconic acid has been definitely synthesized, and been found to differ completely from the tetramethylgluconic acid obtained by the oxidation of the tetramethylglucose. It cannot be made to pass into the tetramethyl- $\delta$ -gluconolactone, and on further oxidation yields tetramethylsaccharic acid,  $\text{CO}_2\text{H}[\text{CH}\cdot\text{OMe}]_4\text{CO}_2\text{H}$ , and not a trimethoxyglutaric acid. Hence the methylated hexose must be a 1:5-oxide, i.e. have a six-atom ring structure, and a similar ring is presumably present in the original glucose.

Similar lines of argument have been adopted in the case of the ordinary forms of xylose, galactose, mannose, rhamnose and lyxose.

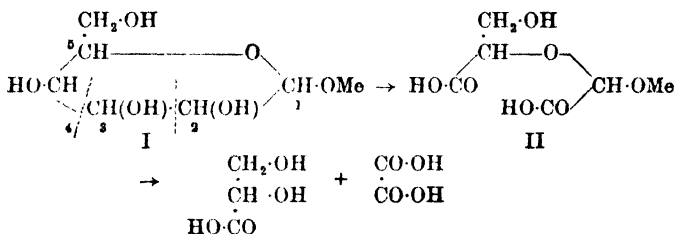
The degradation of the methylated sugar may be represented by means of the following formulæ:



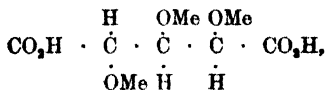
$\text{R} = \text{H}$  for a pentose and  $\text{R} = \text{CH}_2\cdot\text{OMe}$  for a hexose.

A further proof of the pyranose ring in  $\alpha$ -methylglucoside

and  $\alpha$ -methylmannoside is afforded by a study of the products formed by the successive action of per-iodic acid and bromine or of barium hypobromite on these compounds (*Jackson and Hudson, J. A. C. S., 1936, 378*). A rupture occurs between carbons numbered 2 and 3 in the original ring, I, and C<sub>3</sub> is completely eliminated. The product, II, after hydrolysis by hot water and oxidation with bromine gives oxalic and *d*-glyceric acid.



***d*-Fructose.**—This is also to be regarded as belonging to the pyranose series. It yields two stereo-isomeric  $\alpha$ - and  $\beta$ -methylfructosides, both of which are crystalline. The  $\beta$ -compound is readily methylated and from the product a crystalline tetramethylfructose can be obtained. This compound is very stable when compared with the tetramethylated aldoses; bromine water is practically without action, but digestion with nitric acid converts it into a carboxylic acid, trimethylfructuronic acid, by the oxidation of a terminal  $\text{CH}_2\text{OMe}$  group to  $\text{CO}_2\text{H}$ . The acid yields crystalline methyl and ethyl esters, and on further oxidation with acidified permanganate gives *d*-2:3:4-trimethyl- $\delta$ -arabonolactone, the optical enantiomorph of the lactone obtained by the action of bromine water on *l*-trimethylarabinose (p. 915) and finally *d*-arabo-2:3:4-trimethoxyglutaric acid (the enantiomorph of the final oxidation product of *l*-trimethylarabinose). The formation of this dibasic acid,

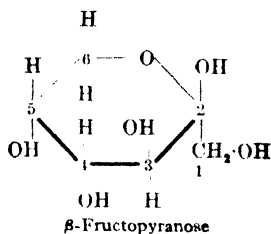
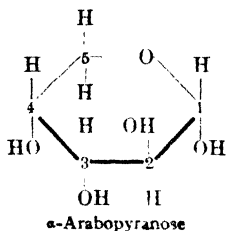
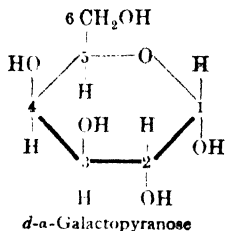
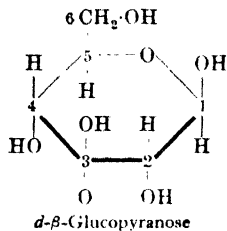


proves that the ring formation which unites carbon atom No. 2 (the carbonyl group of the open-chain ketose mole-



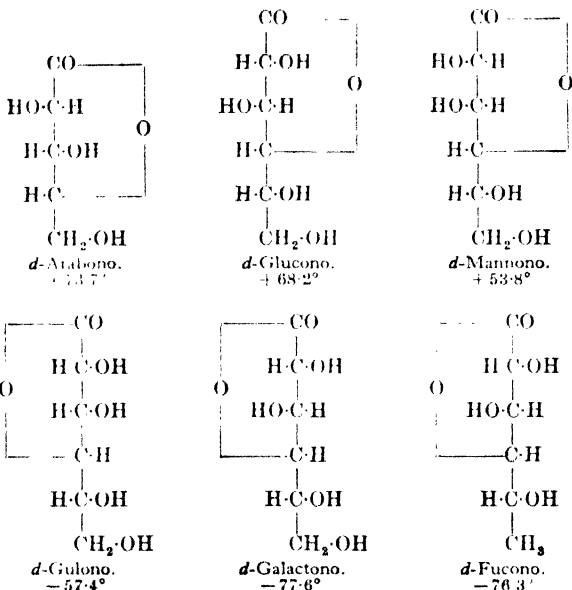
cule) cannot involve positions 3, 4 or 5, and must therefore be between 2 and 6, and hence *d*-fructose must contain a six-atom ring.

The perspective formulæ (*Haworth*) for a few monosaccharides are as follows:



The only differences between an  $\alpha$ - and a  $\beta$ -compound is in the arrangements of the groups attached to the C atom next, in clockwise order of arrangement, to the O atom of the ring.

A confirmation of the pyranose structure of the stable monoses is found in a study of their optical rotations and *Hudson's Lactone Rule* (J. A. C. S., 1910, 338). Hudson reviewed the physical properties of some 24 crystalline lactones derived from sugars, and drew the conclusion that, using the ordinary projection formulæ for the  $\gamma$ -lactones of the monocarboxylic acids derived from or related to simple aldoses, when the oxide ring of the lactone is formed by engaging an OH group on the right side of the carbon chain the optical rotation is enhanced in the dextro sense, and conversely when the OH engaged is on the left of the projection formula of the acid the optical rotation of the  $\gamma$ -lactone is increased in the lævo direction. A few examples are:



The same generalization holds good also for *Fischer's* synthetic mannoheptonolactones and manno-octonolactone. If, however, it is attempted to include in the rule the aldoses and their monomethyl ethers, with their formulæ based on a butylene oxide structure, numerous exceptions are encountered. On the other hand, if they are represented with an amylene oxide or pyranose structure, complete agreement with Hudson's rule follows (*Drew and Haworth*, J. C. S., 1926, 2303), and so far no exception to Hudson's rule has been met with in the case of the known aldoses, their methyl derivatives and all the corresponding lactones whether  $\gamma$  or  $\delta$ .

The spatial configurations given to the  $\alpha$ - and  $\beta$ -compounds are based on the fact that, according to *Boeseken*, the presence of hydroxyl groups attached to two adjacent carbon atoms causes the hydroxyl compound to produce appreciable exaltation in the electrical conductivity of an aqueous solution of boric acid, and the effect is still more marked if the two hydroxyls are spatially adjacent, e.g. on the same side of the molecule. Experiments made with the  $\alpha$ - and  $\beta$ -glucoses corresponding with the  $\alpha$ - and  $\beta$ -glucosides show that the

$\alpha$ -compound produces a greater exaltation than the  $\beta$ -, and hence the configuration represented, viz. with the OH groups in 1 and 2 on *opposite* sides of the molecule, is given to the  $\beta$ -compound, and to the  $\alpha$ -compound is ascribed the configuration in which the two OH groups attached to C atoms 1 and 2 lie in the same plane (B., 1913, 2612). For further examples of the effect of hydroxy compounds on the electrical conductivity of boric acid cf. Abs., 1915, ii, 136, 667, 668; *Irvine and Steele*, J. C. S., 1915, 1221.

## 2. FURANOSE SERIES

*Fischer's*  $\gamma$ -methylglucoside and the two stereo-isomeric  $\gamma$ -ethylglucosides\* (p. 912) differ markedly in chemical properties from the  $\alpha$ - and  $\beta$ -compounds, and are hence structurally different. Similar  $\gamma$ -methyl derivatives have been obtained from most of the ordinary aldoses and ketoses by adopting a method similar to that used by *Fischer*, viz. by condensing the sugar and methylalcohol *at room temperature* in the presence of 1 per cent hydrogen chloride. These  $\gamma$ -methylated sugars exist in two stereo-isomeric forms ( $\gamma$  and  $\delta$ ) analogous to the  $\alpha$ - and  $\beta$ -methyl compounds. The non-alkylated  $\gamma$ -sugars have never been isolated as they are extremely labile and readily pass over into the more stable  $\alpha$  and  $\beta$  forms (pyranose). The existence of two stereochemical forms of the labile sugar is however probable as *Schulbach and Huntenberg* (B., 1927, 1487) have isolated two distinct pentabenzoyl derivatives of  $\gamma$ -glucose. These compounds have  $[\alpha]_D = +58.6^\circ$  and  $-52.6^\circ$ . The rotations of  $\alpha$ - and  $\beta$ -glucose are respectively  $+110^\circ$  and  $+17.5^\circ$  and their pentabenzoyl derivatives  $+107.6^\circ$  and  $+23.5^\circ$ .

The five-atom ring or furanose structure originally attributed to the  $\alpha$ - and  $\beta$ -methylglucosides has now been assigned (*Baker and Haworth*, J. C. S., 1925, 365; *Haworth* and others, 1927, 1241, 2432) to the  $\gamma$ -glucoside, and all labile or  $\gamma$ -compounds are represented by similar formulæ. So far no  $\gamma$ -sugar

\* The four isomeric ethylglucosides may simply be termed  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ , the  $\alpha$  and  $\beta$  being stereo-isomeric pyranose compounds and the  $\gamma$  and  $\delta$  similarly related furanose derivatives. *Haworth and Porter* (J. C. S., 1929, 2796) prefer to call the  $\alpha$ - and  $\beta$ -compounds  $\alpha$ - and  $\beta$ -ethylglucopyranosides and the  $\gamma$ - and  $\delta$ -compounds  $\alpha$ - and  $\beta$ -ethylglucofuranosides. The melting-points and specific rotations  $[\alpha]_D$  are respectively  $113^\circ$ - $114^\circ$ ,  $+160^\circ$ ;  $73^\circ$ ,  $-33.4^\circ$ ;  $82^\circ$ - $83^\circ$ ,  $+98^\circ$ ;  $59^\circ$ - $60^\circ$ ,  $-86^\circ$ .

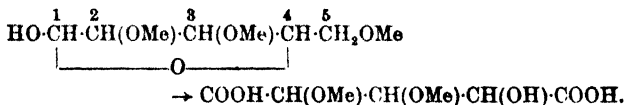
has been detected in natural products\* and no indication of  $\gamma$ -glucose residue in any of the di- or poly-saccharoses has been adduced. On the other hand the fructose portion of cane sugar is almost undoubtedly a  $\gamma$ -fructose (fructo-furanose) residue.

The arguments used in favour of the furanose structure of the  $\gamma$ -sugars are:

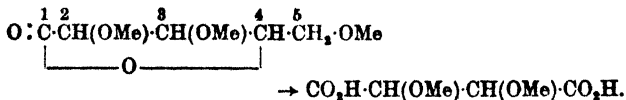
1. The  $\gamma$ -methylglucoside when fully methylated and then hydrolysed yields a  $\gamma$ -tri (or tetra) methyl sugar, and when this is oxidized with bromine water a lactone is formed, which can be shown to be a  $\gamma$ -lactone from its relatively slow rate of hydration. Thus from  $\gamma$ -methylarabinoside a trimethyl  $\gamma$ -arabinose is formed, and this yields a crystalline trimethyl-arabonolactone quite different from that obtained from the  $\alpha$ - or  $\beta$ -methylarabinoside, and difficult to hydrate.

$\gamma$ -Methylglucoside yields a tetramethyl- $\gamma$ -glucose different from the ordinary 2 : 3 : 4 : 6-tetramethyl compound obtained from the  $\alpha$ - and  $\beta$ -methylglucosides, and with bromine water yields a  $\gamma$ -lactone.

2. The  $\gamma$ - or furanose structure of the methylated lactones is confirmed by a study of their oxidation products with nitric acid or of the oxidation products of the methylated sugars. The trimethyl- $\gamma$ -arabinose on oxidation yields 2 : 3-dimethoxy-4-hydroxyglutaric acid. This indicates that the methyl groups are in positions 2, 3, and 5 (the last being eliminated during oxidation of the  $\text{CH}_2\cdot\text{OMe}$  to  $\text{CO}_2\text{H}$ ) and the oxide ring occurs between positions 1 and 4.



When the corresponding 2 : 3 : 5-trimethylarabono- $\gamma$ -lactone is oxidized the product is dimethyl-*d*-tartaric acid (dimethoxy-succinic acid).



\* But the mutarotation of aqueous solutions of galactose indicates the presence of other substances in addition to the  $\alpha$  and  $\beta$  pyranose forms, in all probability two furanose sugars.



In addition to the ordinary aldoses given in Chap. XIV, A., a number of other monosaccharides have been found in nature—usually as anhydrides comparable with the glucosides—and numerous other monosaccharides have been synthesized in the laboratory.

**Vaccilin**, which occurs in cranberries, is glucose-6-benzoate. **Digitoxose** from the leaves of foxglove is a desoxy-methyl-

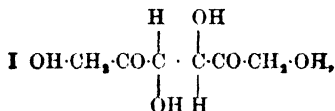
H H H  
 $\text{CH}_3 \cdot \overset{\cdot}{\underset{\cdot}{\text{C}}} \cdot \overset{\cdot}{\underset{\cdot}{\text{C}}} \cdot \overset{\cdot}{\underset{\cdot}{\text{C}}} \cdot \text{CH}_2 \cdot \text{CHO}$ , and stereochemically has no  
 OH OH OH

relationship to any of the natural hexoses, but to *d*-allose and *d*-altrose.

**Cymarose** as a glycoside in Canadian hemp is the 3-methyl ether of digitoxose. **Apiose** occurs in parsley as the glycoside apiin and has the structure  $(\text{OH} \cdot \text{CH}_2)_2 \text{C}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{CHO}$ .

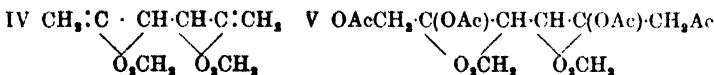
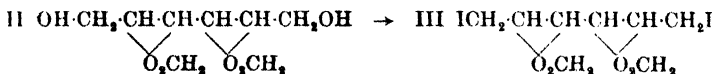
**Digitalose**, isomeric with cymarose, derived from digitalin is  $\text{CH}_3 \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OMe}) \cdot \text{CHO}$ .

**5-Ketofructose** (5-fructonose), I,



can be obtained by the following series of reactions:

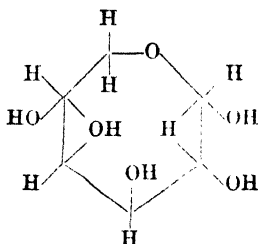
Mannitol  $\rightarrow$  2 : 3 : 4 : 5-dimethylene ether II, di-iodide III, diene IV, tetra-acetate V by treatment with  $\text{Pb}(\text{OAc})_4 \rightarrow$  complete hydrolysis, give the diketose I.



This sugar reduces *Fehling's* solution in the cold, gives crystalline phenylhydrazone and osazone and can be fermented by yeast.

**Septanoses**, monosaccharides with a seven-membered ring

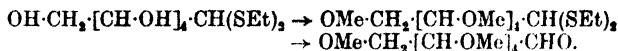
(A., 1933, 507, 138) and a stability comparable with that of the furanose ring.



The structure is proved by the formation of a tetramethyl derivative (after hydrolysis of the pentamethyl compound) and the oxidation of this to a tetramethyl mucic acid.

### 3. SUGARS WITH ACYCLIC STRUCTURES

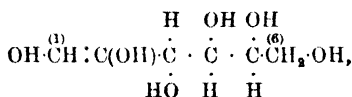
Open-chain aldoses (i.e. *Fischer's* open-chain compounds) probably exist in minute quantities in aqueous solutions of most aldoses, with glucose not more than 0.25 per cent, but mannose may contain as much as 2 per cent, and it has the power of restoring the colour to *Schiff's* reagent (p. 559). The pentamethyl derivatives of glucose, mannose and galactose undoubtedly have the open-chain structure,  $\text{OMe}\cdot\text{CH}_2\cdot(\text{CH}\cdot\text{OMe})_4\cdot\text{CHO}$ , and they readily form diacetals. The method of formation is from the diethylmercaptals, methylating to form the pentamethyl derivatives and removing the  $\cdot\text{SEt}$  groups by means of mercuric chloride:



Similar pentacetyl and pentabenzoyl compounds, and also an open-chain pentacetylfructose (J. A. C. S., 1929, 2188; B., 1930, 1551) have been obtained by similar methods, and another method is to acetylate the oxime of the sugar to a hexacetyl derivative and then hydrolyse with oxalic acid to the pentacetylhexose (:N·OAc replaced by :O) (J. A. C. S., 1934, 1804; 1936, 1781; Bio. J., 1936, 374). Heptacetyl derivatives,  $\text{AcO}\cdot\text{CH}_2(\text{CH}\cdot\text{OAc})_4\cdot\text{CH}(\text{OAc})_2$ , are also stable (J. A. C. S., 1935, 2498).

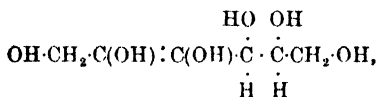
**Action of alkalis on hexoses.**—*Lobry de Bruyn* (B., 1895,

3078; Rec., 1897, 274) found that dilute alkalis can bring about interconversion of glucose, fructose and mannose, and Wohl and Neuberg (B., 1900, 3095) proved that starting with any one of the above hexoses an equilibrium mixture is obtained, and explained the change as due to the formation of an enol which is the same for all three hexoses, viz.

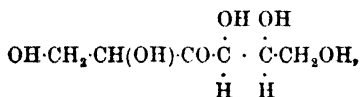


as C atoms 3, 4, 5 and 6 are the same in all three sugars. For differences in action of sodium and calcium hydroxides cf. A., 1936, 525, 221.

Fructose can give rise to a 2nd enol,



and this can revert either to fructose or to new ketose termed **glutose**,



which has been isolated and examined (J. Biol., C., 1926, 68, 1). It has the carbonyl group in position 3, is not fermentable, does not form a hexose phosphate, and is not utilized by a diabetic patient. The treatment with mild alkalis has proved useful for the isolation of new sugars.

When very concentrated alkalis are used the products are **saccharinic acids**,  $\text{OH} \cdot \text{CH}_2 \cdot [\text{CH} \cdot \text{OH}]_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2\text{H}$ , formed by the oxidation of one part of the hexose molecule and the reduction of another (cf. Cannizzaro Reaction, p. 489).

Most sugars with weak alkalis yield methylglyoxal,  $\text{CH}_3 \cdot \text{CO} \cdot \text{CHO}$ , which can be removed by distillation. (For full discussion cf. Nef, A., 1907, 357, 301.)

Concentrated ammonia saturated with zinc chloride gives methylglyoxaline with many sugars,  $\begin{array}{c} \text{CMe} \cdot \text{NH} \\ || \\ \text{CH} - \text{N} \end{array} \begin{array}{l} \diagup \\ \diagdown \end{array} \text{CH}$  (Windaus,



B., 1906, 3886; 1907, 799), and the corresponding carboxylic acid ( $\text{CO}_2\text{H}$  in place of  $\text{CH}_3$ ), imidazole-4-carboxylic acid, is formed from glucose and ammonia saturated with cupric hydroxide (*Parrod*, *Annales*, 1933, 19, 205).

**Synthesis of a hexopyranose from a pentafuranose.**—Although so far it has not been found possible to synthesize a tetramethylhexose from *d*-tartaric acid, it has been found possible to synthesize *l*-tetramethyl-glucosyl- $\delta$ -lactone and -mannosyl- $\delta$ -lactone from *l*-trimethylarabofuranose by the series of reactions given on p. 927 (*Haworth and Peat*), and from these lactones the corresponding tetramethylated hexoses can be obtained by reduction.

## B. Oligo-saccharides

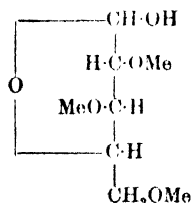
The disaccharides can be regarded as analogous to the methylglucosides, another hexose molecule playing the part of the methyl alcohol. Thus the reducing group of one molecule of hexose forms an anhydride by reacting with a hydroxyl group of a second hexose molecule, either similar to or different from the first. The second hexose group in the majority of cases retains its own reducing group intact, the condensing hydroxyl group being situated lower in the carbon chain. In a few cases, e.g. sucrose, the reducing group of the second hexose residue is involved in the condensation, and these form the group of non-reducing disaccharides. The former group—the reducing disaccharides—have reducing properties, exhibit mutarotation, and yield osazones.

The true structure of a disaccharide can only be settled after the following points have been established:

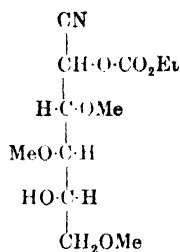
1. The nature of the monosaccharides—whether aldoses or ketoses—taking part in the condensation. It is not only necessary to determine whether these are glucose, mannose, fructose, &c., but also whether they belong to the furanose or pyranose type, and whether the *d* or *l* form.

2. If the reducing group of the second hexose molecule does not participate in the union, it is necessary to fix the position of the hydroxyl group which forms the oxide.

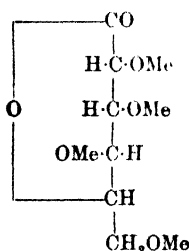
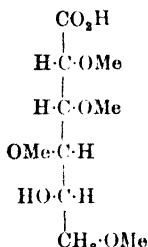
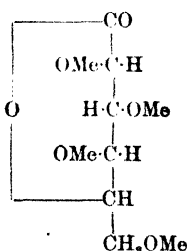
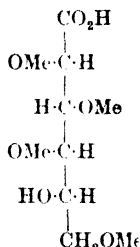
3. As the reducing group of the first hexose molecule takes part in the condensation it is necessary to ascertain if this condensation is of the type of the  $\alpha$ - or of the  $\beta$ -methylgluco-

Trimethyl- $\gamma$ -arabinose

$\xrightarrow{\text{Ethylchloroformate} + \text{KCN}}$



$\xleftarrow{\text{Hydrolysis}}$

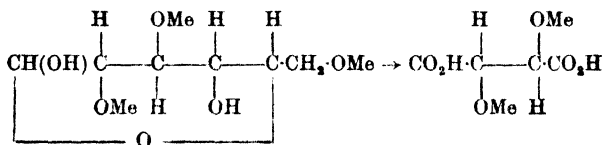
*L*-Tetramethyl- $\delta$ -mannolactone*L*-Tetramethyl- $\delta$ -gluconolactone

side, i.e. is the first hexose residue derived from the  $\alpha$ - or  $\beta$ -form of the hexopyranose, and similarly for the second hexose residue if the reducing group of this is involved.

For purposes of study the fully methylated, octamethyl-derivatives are generally used. These methyl derivatives are quite stable, but it has to be borne in mind that some of the disaccharides are sensitive to alkalis, and hence in their methylation an excess of methyl sulphate should always be present; others, however, are sensitive to acid, and then an excess of

alkali is necessary during methylation. Careful hydrolysis of each fully methylated molecule gives rise to two molecules of methylated monosaccharide (usually hexose), which can be purified by distillation under extremely low pressures and crystallization. In the case of the reducing sugars, one of the hexoses formed is a tetramethyl derivative and the other a trimethyl derivative\* containing a free hydroxyl group, and the first stage is to determine the position of this hydroxyl in the carbon chain of the hexose.

**Maltose** (J. C. S., 1919, 809; 1926, 3094).—The products of hydrolysis of the syrupy octamethylmaltose (b.-pt. 201–203/0.03 mm.) are the well-known 2:3:4:6-tetramethylglucopyranose, melting at 93°–94° (cf. p. 916), and a trimethylglucose which has been shown to be 2:3:6-trimethylglucopyranose. The structure of the latter follows from (a) its conversion into the above-mentioned 2:3:4:6-tetramethyl derivative on further methylation; (b) its oxidation to *d*-dimethyltartaric acid,  $\text{CO}_2\text{H}\cdot\text{CH}(\text{OMe})\cdot\text{CH}(\text{OMe})\cdot\text{CO}_2\text{H}$ ,†

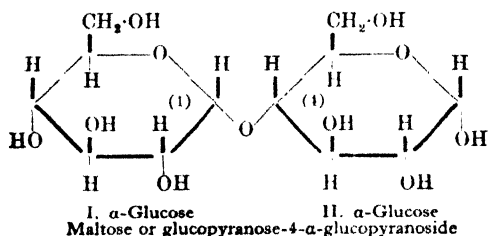


The formation of these two methylated glucopyranoses is in complete harmony with the view that both portions of the maltose molecule contain the pyranose ring, and that the union of the two involves position 1 of the one and position 4 of the other hexose molecule. Although this is probable, there is a little uncertainty as it is just possible that the portion of the molecule yielding the trimethylglucopyranose contains a furanose ring and that the union of the two rings is between carbon atom No. 1 of the first hexose molecule and carbon atom No. 5 of the second. The initial products of hydrolysis would then be 2:3:4:6-tetramethylglucopyranose and 2:3:6-trimethylglucofuranose (a  $\gamma$ -sugar), and, as position 5 is not methylated, this could easily pass into the more

\* One methyl group is removed during hydrolysis, viz. the one corresponding with the methyl group in the methylglucosides, i.e. in position 1 in the pyranose ring not united in position 1 to the second pyranose ring.

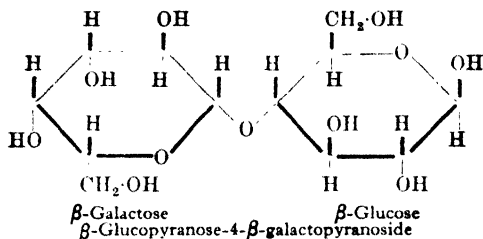
† The isomeric 2:3:4-trimethyl- and 2:3:6-trimethyl-glucoses do not yield dimethyltartaric acids on oxidation.

stable 2:3:6-trimethylglucopyranose, which is the product actually isolated. The question, however, has been definitely settled by an examination of the monobasic acid, maltobionic acid, formed by the oxidation of maltose with bromine water. By this means the oxide ring in one glucose residue is ruptured by the oxidation of the reducing group. When completely methylated, first with methyl sulphate and alkali and finally with methyl iodide and silver oxide, it yields methyl octamethylmaltobionate, and the hydrolysis of this with dilute mineral acid produces hydrolysis of the ester and also a cleavage of the linking between the two hexose groups, and the products are: 2:3:4:6-tetramethylglucopyranose and the lactone of a tetramethylgluconic acid. Its rate of hydration shows this to be a  $\gamma$ -lactone, and it has been proved to be identical with 2:3:5:6-tetramethyl- $\gamma$ -gluconolactone, m.-pt.  $26^{\circ}$ - $27^{\circ}$ . Hence it is position 4 and not 5 in the acid which has the free hydroxyl group, and hence the union of the two hexose groups in maltose is between position 1 in the first and position 4 in the second, and therefore this second group must have its oxide linking between positions 1 and 5, i.e. it must be a glucopyranose residue. The union is of the type of  $\alpha$ -methylglucoside as maltose is completely hydrolysed by maltase, an enzyme which is capable of hydrolysing  $\alpha$ - but not  $\beta$ -glucosides.

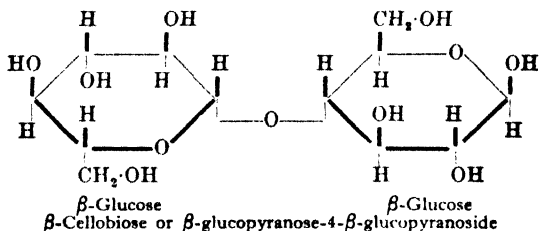


**Lactose** (J. C. S., 1918, 188; 1922, 1213; 1927, 544; B., 1923, 1957).—When lactose is methylated and then hydrolysed, the products are 2:3:4:6-tetramethylgalacto-pyranose, melting at  $71^{\circ}$ - $72^{\circ}$ , and the same 2:3:6-trimethylglucopyranose as is obtained from the methylated maltose, and as lactose is hydrolysed by lactase it must be a  $\beta$ -galactoside. Lactobionic acid, corresponding with maltobionic acid, when methylated and hydrolysed yields 2:3:4:6-tetramethylgalactopyranose

and the same 2:3:5:6-tetramethyl- $\gamma$ -gluconolactone as obtained from the methylated maltobionic acid. It therefore consists of a  $\beta$ -galactose group united in position 1 by means of oxygen to position 4 in a  $\beta$ -glucose residue.



**Cellobiose** (J. C. S., 1921, 193; 1926, 98; 1927, 2809), an intermediate product obtained in the hydrolysis of cellulose (cf. p. 363), when investigated by the method already indicated in the case of maltose, gives identically the same tri- and tetramethylglucopyranoses and the fully methylated cellobionic acid (p. 360) gives the same products as methyl octamethyl-maltobionic acid. As the biose is hydrolysed by emulsin, the specific for a  $\beta$ -glucoside, it undoubtedly consists of two  $\beta$ -glucose groups with an oxide linking between position 1 in the first residue and position 4 in the second.

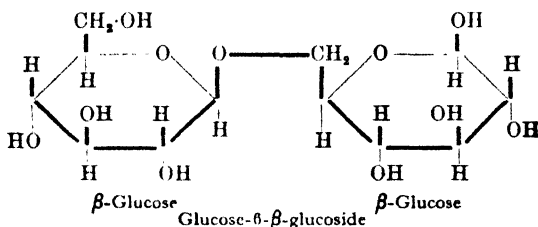


It has been synthesized by *Freudenberg* and *Nagai* (B., 1933, 27) from aceto-bromoglucose and *l*-glucosan with 50 per cent sulphuric acid and its octamethyl derivative by *Irvine* (B., 1930, 1961).

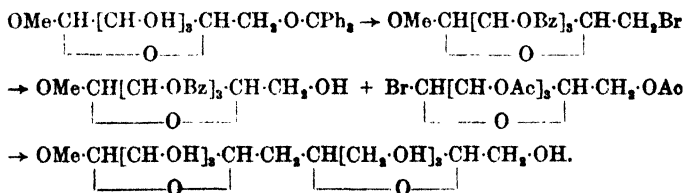
**Gentiobiose** (p. 360) (J. C. S., 1923, 3120, 3125; 1927, 1527) on methylation and hydrolysis gives 2:3:4-trimethyl\* and

\* Me in position 1 is removed during hydrolysis.

2:3:4:6-tetramethyl-glucopyranose, and as it is hydrolysed by emulsin contains two  $\beta$ -glucose residues united by oxygen in position 1 of one residue and position 6 of the other. Confirmation of this is furnished by the oxidation of the sugar to gentiobionic acid, and the hydrolysis of the completely methylated acid to 2:3:4:6-tetramethylglucopyranose and an acid proved to be 2:3:4:5-tetramethylgluconic acid, as it yields an ester but no lactone, and on further oxidation with nitric acid yields tetramethylsaccharic acid,  $\text{CO}_2\text{H}\cdot[\text{CH}\cdot\text{OMe}]_4\cdot\text{CO}_2\text{H}$ .

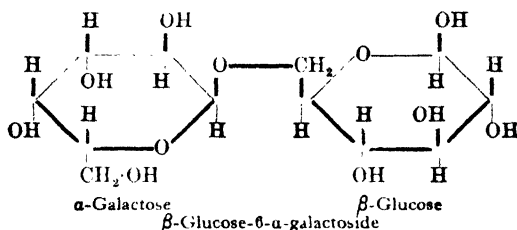


It has been synthesized from *Fischer's* acetobromoglucose and 3:5-benzylidene-1:2-isopropylidene-glucose, and the subsequent removal of  $\text{CH}_3\cdot\text{CO}\cdot$ ,  $\text{C}_6\text{H}_5\text{CH}:$  and  $(\text{CH}_3)_2\text{C}:$  groups (B., 1936, 1219) and another synthesis (*Helferich, Klein and Schäfer, A.*, 1926, 447, 19; 450, 225) is from 6-triphenylmethyl- $\alpha$ -methylglucoside; when benzoylated and treated with phosphorus pentachloride, this gives 2:3:4-tribenzoyl-6-bromo-methyl-glucoside,\* m.-pt.  $122^\circ$ . From this 2:3:4-tribenzoylmethylglucoside can be obtained, and when this is condensed with 2:3:4:6-tetracetyl-1-bromo-glucopyranose and the product hydrolysed carefully to remove acyl groups methylgentiobioside is obtained.



\* The structure of this follows from the fact that on reduction and hydrolysis it yields *iso*-rhamnose,  $\text{CH}_2\cdot\text{CH}[\text{CH}\cdot\text{OH}]_3\cdot\text{CH}\cdot\text{OH}$ .

**Melibiose**, one of the hydrolytic products of raffinose (p. 360), is similar to gentiobiose; its octamethyl derivative yields 2:3:4:6-tetramethylgalactopyranose, and 2:3:4-trimethyl glucopyranose, and the completely methylated melibionic acid on hydrolysis yields 2:3:4:6-tetramethylgalactopyranose and the same 2:3:4:5-tetramethylgluconic acid as is obtained from the methylated gentiobionic acid.



It would thus appear that in trisaccharides and in certain glucosides such as emulsin the hexose residues are united by means of oxygen between the 6th carbon atom (i.e. the side chain of the pyranose ring) of one residue and the first carbon of the second residue.

Further confirmation of the  $\alpha$ - or  $\beta$ -glucosidic structure of the disaccharides mentioned is obtained by a study of their optical rotations. In the following table column 1 gives the specific rotations of the methyl esters of the hexamethyl-monobasic acids derived from the disaccharides, column 2 gives the values for the mixed hydrolytic cleavage products after equilibrium is attained, and the values for the ordinary monomethyl glucosides and galactosides are:

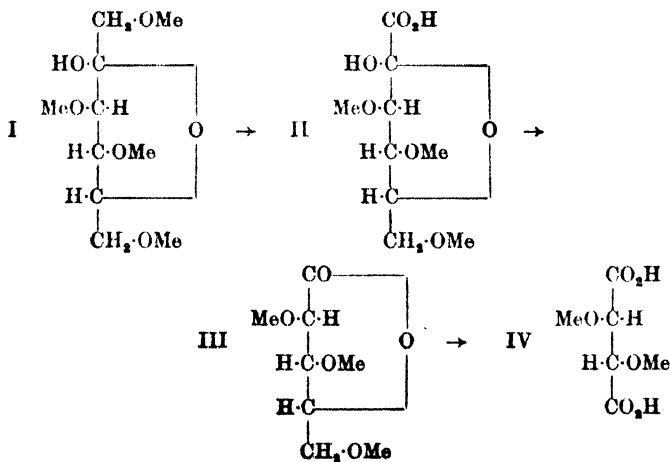
$\alpha$ -methylglucoside	+ 158°	$\alpha$ -methylgalactoside	+ 193°
$\beta$ -methylglucoside	- 34°	$\beta$ -methylgalactoside	- 1°
		1.	2.
1. Methyl octamethylmaltobionate	+ 121°		+ 55°
2. Methyl octamethylmelibionate	+ 106		+ 64
3. Methyl octamethylcellobionate	+ 5		+ 55
4. Methyl octamethyl-lactobionate	+ 34		+ 77

Presumably esters Nos. 1 and 2 are  $\alpha$ - and esters Nos. 3 and 4  $\beta$ -compounds. Further the reduction in the rotation value on cleavage (column 2) of Nos. 1 and 2 can be due to the change of the  $\alpha$ -sugar (high rotation) to the equilibrium mixture of  $\alpha$ - with  $\beta$ -sugar (low rotation) and the enhancement in Nos. 3

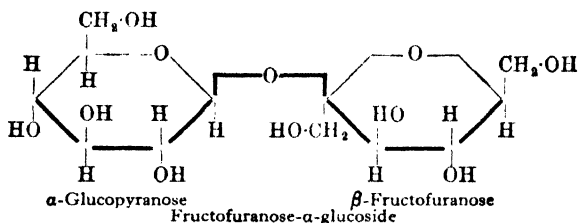
and 4 to the liberated  $\beta$ -sugars passing into an equilibrium mixture of  $\alpha$ - and  $\beta$ -sugars (J. C. S., 1927, 3146).

**Sucrose** (J. C. S., 1916, 1314; 1920, 199).—Sucrose has no reducing properties, shows no mutarotation, and does not yield an osazone. It is thus an anhydro compound in which the reducing group of each of the two components is involved. When hydrolysed the final products are *d*-glucopyranose and *d*-fructopyranose. When, however, its octamethyl derivative is hydrolysed the products are 2:3:4:6-tetramethylglucopyranose, and 1:3:4:6-tetramethylfructofuranose (I), obtained pure as a liquid with  $[\alpha]_D = +31.7^\circ$  by hydrolysis of heptamethylsucrose and removal, by distillation, of trimethylglucose formed at the same time.

The structure of this furanose has been established: (1) By oxidation to a trimethylfructuronic acid (II) with the elimination of a methyl group indicating the presence of a terminal  $\text{CH}_2\cdot\text{OMe}$  group. This monobasic acid has reducing properties, showing the presence of the ketose reducing group, and this property disappears on complete methylation. (2) On further oxidation with acidified permanganate the acid yields *d*-2:3:5-trimethyl- $\gamma$ -arabonolactone (III), the optical antipodes of that obtained by oxidizing *l*-trimethylarabonofurose, and on still further oxidation with nitric acid *d*-dimethoxysuccinic acid (IV) is obtained.

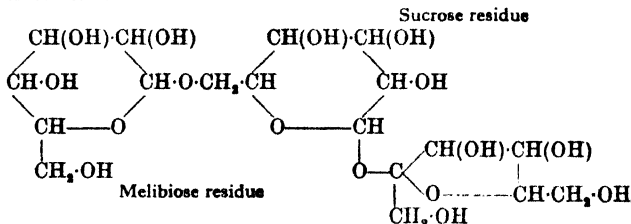






**Synthesis of Sucrose.**—*Pictet* and *Vogel's* claim (Helv., 1928, 436) to have synthesized octacetylsucrose by condensing tetracetyl-fructo-furanose with tetracetylglucopyranose has not been confirmed, but an *isosucrose octacetate* is formed by recondensing the products formed by splitting octacetylsucrose with acetyl bromide. It has m.-pt.  $129^{\circ}$ – $131^{\circ}$ ,  $[\alpha] + 19.3$ , is somewhat unstable, and is probably  $\beta$ -glucose- $\beta$ -fructofuranoside (*Irvine* and *Oldham*, J. A. C. S., 1929, 1279, 3609). According to *Klages* and *Niemann* (A., 1937, 529, 185), all attempts to synthesize an  $\alpha$ -glucoside- $\beta$ -fructofuranoside give negative results, but in some cases an isomeric  $\beta$ -glucose- $\alpha$ -fructofuranoside is formed.

**Raffinose and Gentianose** (J. C. S., 1923, 3125; 1927, 1527, 3146).—Raffinose on methylation takes up 11 methyl groups and on hydrolysis of the methylated product the following compounds can be isolated, 1:3:4:6-tetramethylfructofuranose, 2:3:4-trimethylglucopyranose and 2:3:4:6-tetramethylgalactopyranose. The structure of the original sugar is hence



since when hydrolysed with emulsin it yields galactose and sucrose and with invertase it yields fructose and melibiose.

Gentianose is similar but contains the gentiobiose residue in place of the melibiose group.

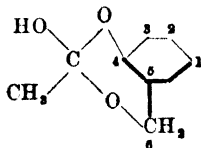
Scamnose is built up of glucose, rhamnose and fructose residues, solanose of glucose, galactose and rhamnose residues

and melezitose is 1- $\alpha$ -glucose-2- $\beta$ -fructofuranose-6- $\alpha$ -glucoside.

**Stachyose**, a tetrasaccharide, present in ash manna and in the tubers of *Stachys tubifera*, is hydrolysed by dilute acetic acid to fructose and a reducing trisaccharide *manninotriose* from which galactose (2 mols.) and glucose (1 mol.) can be obtained. A study of the methyl derivatives of stachyose and of manninotrionic acid prove that the fructopyranose and glucopyranose are united by their reducing groups, that the reducing group of one galactopyranose is linked to C4 of the glucose, that the C6 of the former is combined with the reducing group of the second galactopyranose residue, but whether the linkings are  $\alpha$  or  $\beta$  has not been decided (*Onuki*, 1932).

### C. Acyl and Acetone Compounds of Sugars

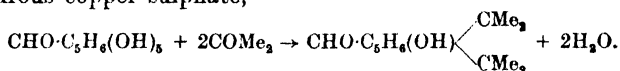
**Wandering of Acyl Groups.**—Numerous cases of the wandering of acyl groups during reactions in which acetyl derivatives of sugars are involved have been noted (for summary cf. Rep., 1934, 172), more particularly under the influence of traces of alkali, e.g. from C1 to C4, from C4 to C6, from C2 to C6, from C3 to C5, and from C3 to C6, and may be explained in certain cases by the formation of an ortho acetic ester, e.g. transference from C4 to C6 by aid of the cyclic ortho-acetate:



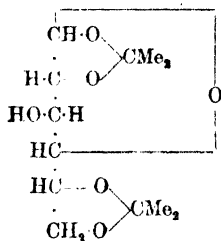
It follows that structures based on experiments made with acetyl derivatives must be accepted with a certain amount of reserve.

The aldoses and ketoses readily condense with acetone, yielding, e.g., glucose-acetone and glucose-diacetone. Many of these are crystalline compounds and some can be distilled under very low pressures. They are to be regarded as isopropylidene derivatives of the sugars, the divalent isopropylidene group  $(\text{CH}_3)_2\text{C}$ : replacing the hydrogen atoms of two hydroxyl groups in the sugar. The two hydroxyl groups are usually attached to two adjacent carbon atoms in the chain, or, if not, they must be spatially adjacent. Di-isopropylidene-glucose is

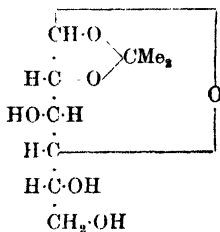
obtained by shaking an acetone suspension of glucose with a small quantity of hydrogen chloride, zinc chloride, or anhydrous copper sulphate,



It has no reducing properties, but contains one free hydroxyl group and yields a monomethyl ether, which, on acid hydrolysis, yields 3-methylglucopyranose. The diacetone compound on partial hydrolysis yields the monoacetone derivative, mono-isopropylidene-glucose, a non-reducing compound, which on methylation and subsequent hydrolysis yields a trimethylglucose, and this on complete methylation and oxidation yields tetramethyl- $\gamma$ -gluconolactone. This proves the 1:4 oxide or furanose structure of the tetramethylglucose and hence of the original mono- and di-isopropylidene compounds.



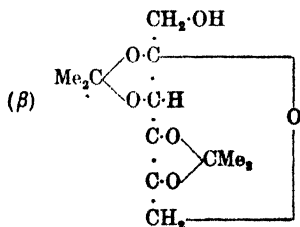
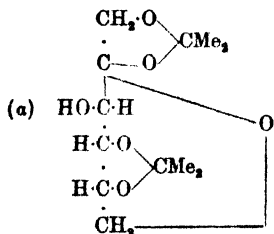
Diacetone glucose



Monoacetone glucose

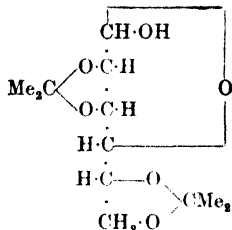
(Cf. J. C. S., 1929, 1329, 1337.)

*d*-Fructose yields two structurally isomeric diacetone derivatives, both of which have been shown to be pyranose derivatives and both are non-reducing.



**Mannose diacetone** is interesting as it exhibits mutarotation and has reducing properties, and hence the reducing group has

not participated in the condensation. It is represented as



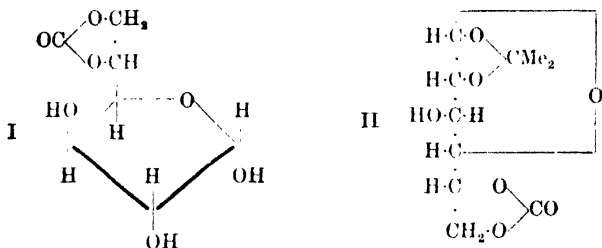
i.e. a furanose although obtained from mannopyranose.

The general conclusion (*Haworth*) based on the known reactions so far studied is that acetone residues condense with appropriately situated (structurally or spatially) hydroxyl groups in any sugar *regardless* of any preformed oxide system in the sugar. The sugar ring adjusts itself to that position (whether 4 or 5) left open after the preferential selection of positions of entry is made by the isopropylidene groups. Thus a change in ring may occur during the formation of acetone derivatives, and has actually been noted in the cases of *d*-glucopyranose, *d*-mannopyranose and *d*-xylopyranose, which yield furanose isopropylidene derivatives. The  $\alpha$ - and  $\beta$ -methylmannopyranosides yield diacetone derivatives with isopropylidene groups in positions 2 and 3, 4 and 6, i.e. the pyranose ring remains intact, and one of the isopropylidene groups is attached to two oxygen atoms which are not linked to adjacent carbon atoms. The two OH groups concerned must, however, be sufficiently near to admit of the ring closure by :CMe<sub>2</sub>. If free methyl alcohol is present during the condensation then the 2 : 3, 5 : 6-diacetone compound is formed and the product is a furanose compound.

With *d*-fructopyranose and *d*-galactopyranose no such change occurs. The usual position of the hydroxyl groups affected is in the *cis*-position and attached to two adjacent carbon atoms, but this is not invariably true as in xylopyranose the hydroxyl groups attached in positions 3 and 5 condense with acetone.

Benzaldehyde can also condense with certain monosaccharides, the O of CHO reacting with the H of two adjacent OH groups. In this case no conversion of a pyranose into a furanose compound occurs, but a furanose with OH group spatially suitable will yield a benzylidene furanose compound.

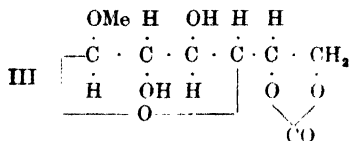
**Sugar carbonates** (*Haworth and Porter, J. C. S., 1929, 2796; 1930, 151*).—Similar to the acetone compounds are the sugar



carbonates, obtained by condensing the sugars with carbonyl chloride in pyridine or mildly alkaline solutions. They are crystalline compounds and unlike the acetone compounds they are unstable to alkalis but much more stable to acids.

The glucofuranose carbonate I is interesting as being the first definite glucofuranose derivative with the free reducing groups to be isolated.

A mixed derivative, glucose-acetone-carbonate II, is formed when a glucose suspension in acetone is treated with carbonyl chloride. It forms large crystals, m.-pt. 143°–145° and  $[\alpha]_D - 64^\circ$ . Digestion with dilute acid in the presence of methyl alcohol eliminates the isopropylidene group and introduces methyl yielding the carbonate of methylglucofuranoside III.



## D. Polysaccharides

**Starch and Cellulose.\***—The two commonest polysaccharides are starch and cellulose; the former on hydrolysis yields maltose and the latter cellobiose, but the final hydrolytic product of both is *D*-glucose, indicating that both polysaccharides are built up of glucopyranose units united in 1 : 4-positions.

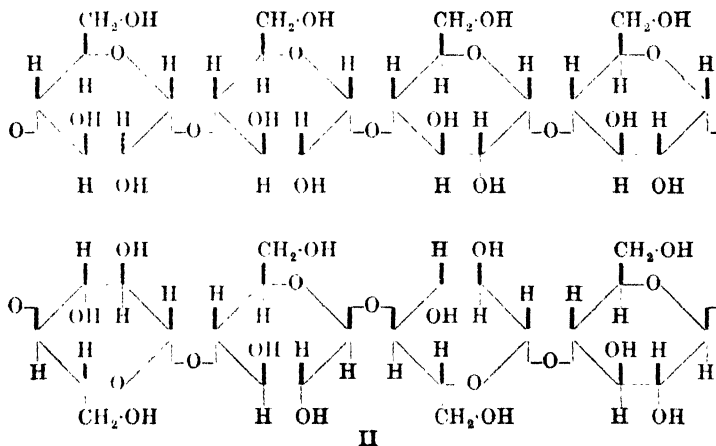
\* 1. *Biochemistry of Cellulose*, Norman, London, 1937.

2. *An Introduction to the Chemistry of Cellulose*, Marshall and Wood, London, 1938.

3. Haworth, C. and I., 1939, 917.

The difference between the two is that in the starch molecule the units are  $\alpha$ -glucopyranose and in cellulose  $\beta$ -glucopyranose, as indicated by the partial hydrolytic products, maltose and cellobiose respectively.

The result of the union of a number of  $\alpha$ -glucopyranose molecules as in maltose results in a structure represented in part by I, a characteristic of which is that the  $\cdot\text{CH}_2\cdot\text{OH}$  group of each glucose residue lies above the plane of the paper; whereas the union of a number of  $\beta$ -glucopyranose groups gives a structure II in which the  $\cdot\text{CH}_2\cdot\text{OH}$  groups alternate between the upper and lower planes, thus producing a more symmetrical configuration. It is clear therefore that the great differences between the chemical and physical properties of starch and those of cellulose are due not to structural but to stereochemical causes, viz. the  $\alpha$ - or  $\beta$ -linking of the glucopyranose residues.



The repetition of  $\alpha$ -glucopyranose (or maltose) units in a long chain yields a model which differs in a zigzag or spiral fashion from the more or less straight line furnished by the union of cellobiose residues in cellulose. This may account for the marked differences in the X-ray diagrams for natural cellulose and starch. The former yields a regular pattern, whereas the latter does not readily. The size of cell required by the X-ray diagram for cellulose agrees with the stereochemical structure given above.

Many attempts have been made to ascertain the number of maltose or cellobiose units in starch and cellulose respectively; in other words, the molecular weights of the two compounds. Many of these are physical, e.g. the viscosity method (*Staudinger*, cf. B., 1936, 819), the sedimentation method of the ultra-centrifuge and osmotic pressure of acetyl and methyl derivatives.

The different methods give different results, varying from 15 to 500 thousand as the molecular weight, and it is agreed that the laws which hold good for short-chain molecules may not hold good for complex aggregates.

A chemical method used by *Haworth* and his co-workers (J. C. S., 1932, 2270) is to methylate the complex carbohydrate and then to determine the relative amounts of tri- and tetramethyl glucoses formed on hydrolysis. It is clear that only one terminal methylated glucopyranose unit can yield a tetramethylglucose; all the inner units and one terminal\* will yield the trimethylglucose. Adopting this method the result indicates approximately 100 to 200 glucopyranose units in cellulose. This must be regarded as the lowest limit possible, as partial decomposition during the reaction is not completely excluded. (For criticisms cf. *Neumann*, B., 1937, 710.) The physical methods indicate much larger molecules, and it is possible that these larger aggregates may be due to the union of the smaller molecules by co-ordinate links or by physical forces.

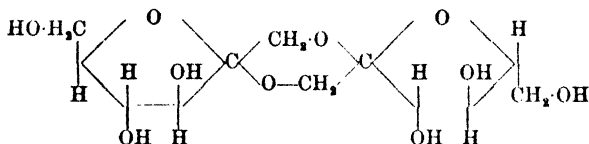
Starch molecules contain both phosphorus and silicon, but very little is known of the amounts or the method of union. *Waldschmidt* and *Leitz* suggest the union of several polysaccharide molecules into complexes by phosphoric ester links. These are broken by the enzyme amylophosphatase, yielding amyloses and liberating inorganic phosphates. Both  $\alpha$ - and  $\beta$ -amylose when examined by *Haworth's* methylation process give similar results, viz. 26-30 glucose units or a molecular weight of about 5000, and starches of different origins give similar results. It is claimed that the value is too low for  $\alpha$ -amylose as during the various processes involved in methylation some  $\beta$ -amylose degradation may occur. The viscosity method gives results 5-20 times that just indicated, and shows higher values for  $\alpha$ - than for  $\beta$ -amylose.

\* The one with the OMe attached to the C adjacent to the O of ring and hence readily hydrolysed like the methylglucosides.

When examined by the methylation method the different dextrans give numbers varying from 17 units for  $\alpha$ -amylodextrans to 5 for the simplest dextrans, and many exhibit a tendency towards molecular aggregation.

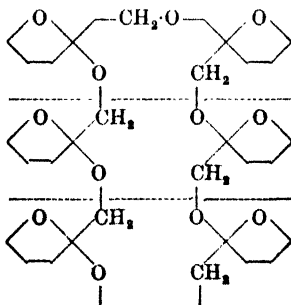
Potato starch itself has slight copper-reducing properties, about  $\frac{1}{700}$  of that of maltose, and it is claimed that the chain length of a given starch—and also of its fission products—can be determined by its copper-reducing value. This method indicates 1470 glucose units for potato starch and 460 for maize starch.

**Inulin** is built up of fructofuranose residues as the main product of hydrolysis of the completely methylated carbohydrate is 3 : 4 : 6-trimethylfructofuranose. Characteristic is the readiness with which it hydrolyses under the influence of mild reagents, e.g. when boiled with water its molecular weight diminishes from about 5000 to half of this in 28 minutes. It also yields a bioseanhydride, viz. 1 : 2-difructofuranose anhydride:



The method of methylation and subsequent hydrolysis indicates 30 fructofuranose units, and this conclusion is confirmed by ebulliscopic and osmotic pressure methods for determining molecular weight.

The structure cannot be represented by a plane formula, and the following formula has been suggested by *Haworth*:



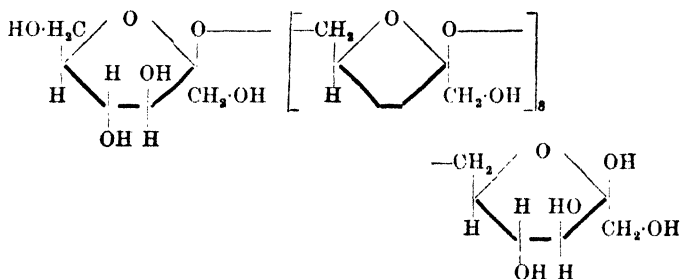
repeated to give 30 furanose units.



The dotted lines indicate the direction of cleavage in the formation of the anhydride.

It is also possible that the molecule is built up of biose-anhydride units united by co-ordinate links, viz. the O of the central ring donating to H of the central ring of another unit.

A water-soluble polysaccharide is found in the leaves of certain grasses. It is built up entirely of fructofuranose units united in positions 2 and 6, and as the number of units is 10 the formula may be represented as follows:



**Lichenin**, present in the cell wall of many lichens, appears to be built up of 80 glucopyranose units, and **xylan**, a constituent of esparto and other grasses, yields on hydrolysis 93 per cent of xylopyranose and 7 per cent of arabofuranose and consists of a terminal arabofuranose unit and 19 xylofuranose units. During the breakdown of the molecule the arabofuranose residue is first removed and the xylodextrin formed contains xylopyranose units only, as the hydrolytic products of the methylated carbohydrate are mainly dimethyl-, with a little trimethyl-xylopyranose formed from a terminal xylopyranose residue.

**Synthetic polysaccharides** are formed by the action of moulds (*Penicillium*) on nutrient media containing glucose and other sugars. Thus *P. Charlesii* with glucose yields two carbohydrates, one composed of mannose units and termed **mannocarolose** and the other of galactose units.

Molecular weight determinations of the acetyl derivative of mannocarolose in *o*-cresol corresponds with a complex of 9 mannose units, and the methyl derivative on hydrolysis yields tetramethylmannopyranose (13 per cent) and 2:3:4-trimethylmannopyranose (87 per cent), and it is suggested

that the units are united in 1:6-positions by means of an  $\alpha$ -linking (*Haworth*, *Biochem. J.*, 1935, 612).

**Varianose**, obtained by the growth of *P. varians* on glucose solutions containing nutrient media, has three types of units, viz. glucose, galactose and idose or altrose, all of the pyranose types and in the relative proportions 1:8:1 (*Bio. J.*, 1935, 2668).

**Immuno-polysaccharides**.—Many organisms, e.g. *Pneumococcus*, *streptococcus*, *gonococcus*, during their growth produce compounds of polysaccharide nature which have active immunity against specific diseases (cf. *J. Exp. Med.*, 1936, **64**, 557).

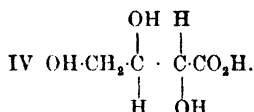
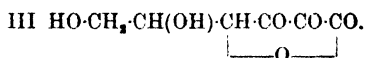
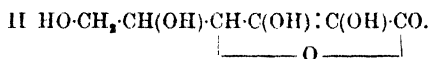
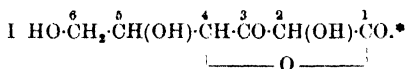
Other natural polysaccharides are the mannan and galactans built up of mannose and galactose units. *Tubera salep* mannan contains the mannan units combined in the same way (1:4) as glucose units in starch and contains probably 60 units.

**Plant Gums and Mucilages**.—These are polysaccharide in structure, but usually contain a diversity of sugar units joined together by glucosidic links (*C. and I.*, 1937, 724). The number of different sugars may be as high as five and of both pyranose and furanose types, e.g. glucose, mannose, galactose, fructose, xylose, arabinose, rhamnose and fucose, and usually glycuronic or galacturonic acid. Gum arabic has been shown to contain as part of its molecule the aldobionic acid formed from glycuronic acid linked glucosidually to the 6th C atom of a galactose residue.

## E. Ascorbic Acid and Related Compounds

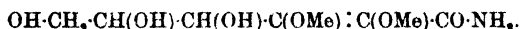
**Vitamin C, l-ascorbic acid** (*Chap. LXVIII*), has been shown to be the lactone of the enolic form of a  $\beta$ -ketonic acid related to the sugars. It contains 4 hydroxyl groups, 1 primary, 1 secondary, and 2 tertiary. Two of these must be in 1:2- or 1:3-positions as it yields an acetone condensation product. It also yields a diphenylhydrazone and is readily oxidized by iodine to a 2:3-diketohexonic acid III, and on further oxidation with sodium hypoiodite to oxalic and trihydroxybutyric acid (*l*-threonic acid) IV, and finally to *d*-tartaric acid. The

formula suggested by *Haworth* and his co-workers is represented by I or the enolic form II:

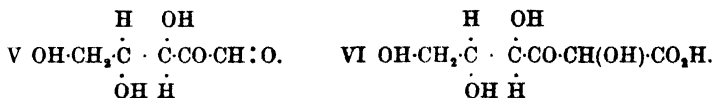


The presence of the olefine link is proved by the action of ozone on the 2:3-dimethyl ether when a neutral dimethyl ester is formed,  $\text{C}(\text{OMe}) : \text{C}(\text{OMe}) \rightarrow \text{CO}_2\text{Me} \cdot \text{CO}_2\text{Me}$ . Diazomethane yields first the 3-methyl and then the 2:3-dimethyl ether.

Ascorbic acid, as its name indicates, has acidic properties and forms salts. These are not formed by the fission of the lactone ring, but at the expense of the two tertiary hydroxyl groups. By the action of ammonia on the 2:3-dimethyl ether the ring is broken and the true amide formed:



The structure of the acid has been confirmed by its synthesis. *Haworth*, *Hurst* and others (J. C. S., 1933, 1419), starting with *l*-xylosone V, formed the cyanhydrin (hydroxy nitrile) and by hydrolysis the hydroxyketonic acid VI, which in its enolic form yields a lactone (Formula II, above) identical with ascorbic acid:



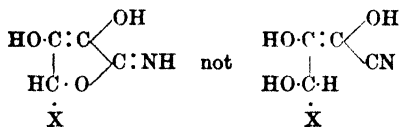
The methods available for obtaining ascorbic acids are:

1. The osone method as used by *Haworth* (see above). Numerous acids analogous to *l*-ascorbic acid have been synthesized by this method (J. C. S., 1933, 1419; 1934, 62, 1192).

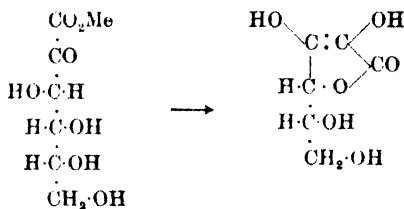
The structure of the additive compound of the osone and

\* In all these formulae the H atoms attached to carbons 4 and 5 are on the opposite sides of the molecule.

hydrogen cyanide is probably that of a cyclic imine and not of an acyclic cyanhydrin, viz.:



2. By the action of sodium methoxide on methyl esters of 2-ketonic acids, e.g. methyl 2-ketoglutarate yields *d*-arbo-ascorbic acid:



The ketonic acid can be obtained by several methods, e.g. carefully regulated oxidation of a ketose, e.g. *d*-sorbitose or *d*-fructose with dilute nitric acid or by oxidizing the 2 : 3 : 4 : 6-diacetone derivative of a ketose to a carboxylic acid, removal of the acetone residues, and the formation of the ketonic acid (*Reichstein and Gr  nner*).

3. The oxidation of osones to keto-acids and the rearrangement of these as under (2).

4. Condensation of *d*-glucose with ethyl glycollate in the presence of sodium cyanide and in the absence of air yields glucoheptoascorbic acid, and the method is applicable to all aldoses and their acetates as these latter are hydrolysed during the reaction.

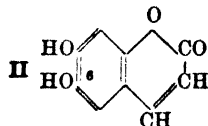
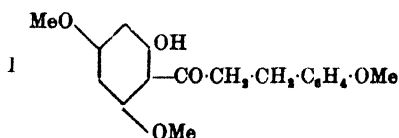
## F. Glycosides

Many complex hydroxy compounds occur naturally—especially in the vegetable kingdom—in combination with glucose or another sugar. As glucose was the common sugar present these were termed glucosides—analogueous to the  $\alpha$ - and  $\beta$ -methylglucosides, but with a complex in place of the methyl group. As further examination has shown that a great variety of sugars occur in nature in the form of these anhydrides, the

generic term glycosides has been adopted. Examples of these glycosides are met with in the plant-colouring matters (the anthocyanins and flavone colouring matters, Chap. LXIV), in the cardiac poisons and in the saponins (Chap. LXII).

The function of the sugar group is probably to render the compound more readily absorbable in the plant tissue.

On hydrolysis—often by an enzyme in the tissue—the glycoside yields the sugar or sometimes a mixture of sugars and the hydroxy compound—very frequently a complex polyhydroxy cyclic compound, e.g. phloridzin,  $\text{XO} \cdot \text{C}_6\text{H}_2(\text{OH})_2 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{OH}$ , yields phloretin,  $\text{C}_6\text{H}_2(\text{OH})_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{OH}$ , and glucose (where X = glucosidyl radical). A simple method of determining to which of the four hydroxy oxygen atoms present in phloretin the glucose radical is attached has been worked out. This consists in completely methylating the compound, then hydrolysing and determining the position of the free hydroxyl group formed by the removal of the methylated glucose radical. When phloridzin is treated in this way the product formed is dimethoxy-hydroxyphenyl *p*-methoxyphenylpropyl ketone,  $(\text{OMe})_2\text{C}_6\text{H}_2(\text{OH}) \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{OMe}$ , which yields a chromone compound when heated with acetic anhydride and sodium acetate and hence has the OH in the *ortho*-position to the long side chain and is therefore I.



from which it follows that the glucose radical is attached to an oxygen atom *ortho* to the ketonic group.

Similarly aesculin, present in horse-chestnuts, yields glucose and aesculetin, 6 : 7-dihydroxy-coumarin, and by the methylation method it can be proved that the glucose radical is attached to the O atom in position 6 (II). Fraxin, which yields glucose and fraxitin, 7 : 8-dihydroxy-6-methoxy-coumarin, can be shown to have the glucose radical attached to O in position 8.

A confirmation of the position of the sugar radical in such compounds is afforded by synthetical methods (cf. *Robinson*, B., 1934, 85).

Among the commoner natural glycosides are:

**Amygdalin**,  $C_{20}H_{27}O_{11}N$  (p. 491), found in bitter almonds, in the leaves of the cherry laurel, in the kernels of the peach, cherry, and other Amygdalaceæ. It crystallizes in colourless prisms, melts at  $200^{\circ}$ , is readily soluble in water, and on hydrolysis with emulsin yields benzaldehyde, *d*-glucose, and hydrogen cyanide. Emulsin is an enzyme which occurs in bitter almonds. It is characteristic of most glucosides that in the plant tissue they are accompanied by an enzyme, which is able in the presence of water to hydrolyse them. Amygdalin may also be hydrolysed by dilute mineral acids.

With concentrated hydrochloric acid it yields *l*-mandelic acid, and with an enzyme contained in yeast (amygdalase) it yields glucose and *l*-mandelonitrile-glucoside. A synthetic *dl*-mandelonitrile-glucoside has been synthesized by the following stages: condensing acetobromoglucose with *dl*-ethyl mandelate, converting the product into the corresponding amide, removal of the acetyl groups by hydrolysis, and elimination of water from the amide by means of  $POCl_3$ . The *dl*-compound is also formed by racemization of the *l*-compound with alkali.

Amygdalin is the commonest of the *cyanogenetic glucosides*, i.e. glucosides which give rise to hydrogen cyanide in plant tissues or on hydrolysis. Some of the other members are: **dhurrin**, *p*-hydroxy-mandelonitrile-glucoside (*Dunstan and Henry*), in the great millet; **phaseolunatin**, acetone-cyanohydrine- $\beta$ -glucoside, in beans of *Phaseolus lunatus*; **lotusin** from *Lotus arabicus*.

**Salicin**,  $C_{13}H_{18}O_7$ , found in varieties of *Salix*, is hydrolysed to saligenin (*o*-hydroxy-benzyl alcohol) and dextrose; **populin** or **benzoyl-salicin**,  $C_{10}H_{22}O_6$  (in varieties of *Populus*), can be prepared artificially from benzoyl chloride and salicin.

**Arbutin**,  $C_{12}H_{16}O_7$ , and **methyl-arbutin**,  $C_{13}H_{18}O_7$ , present in the leaves of the bear-berry, &c., yield glucose and quinol or methyl-quinol respectively.

**Hesperidin**,  $C_{22}H_{26}O_{12}$ , which is contained in unripe oranges, &c., can be decomposed into glucose, hesperetic acid (isomeric with ferulic acid, p. 533), and phloroglucinol.

**Phloridzin**,  $C_{21}H_{24}O_{10}$ , found in the bark of fruit-trees, yields glucose and **phloretin**,  $s-(OH)_3 \cdot C_6H_2 \cdot CO \cdot (CH_2)_3 \cdot C_6H_4 \cdot OH$  (*p*), and this latter, in its turn, phloretic acid and phloroglucinol (p. 486). For structure cf. J. C. S., 1930, 21. Both induce glycosuria (a functional derangement of the liver, producing temporary diabetes) in animals.

**Digitonin, digitalin, and digitalein** are three glycosides which, together with **digitoxin** (the most important constituent from a pharmacological point of view), are present in the digitalis of commerce (cf. Chap. LXII, E.).

**Coniferin**,  $C_{16}H_{22}O_8 + 2H_2O$ , contained in the cambium sap of the Coniferæ, yields glucose and coniferyl alcohol on hydrolysis, and serves for the preparation of vanillin (p. 498).

**Indican** (Chap. XLI, C.) is indoxyl-glucoside.

**Syringin**, the glucoside of Syringa, is a methoxy-coniferin derivative.

**Myronic acid**,  $C_{10}H_{17}O_9NS_2$ , is present as potassium salt (*Sinigrin*),  $C_{10}H_{16}KO_9NS_2 \cdot H_2O$  (glistening needles), in black mustard seed. It is hydrolysed by baryta water, or by myrosin, an enzyme present in mustard seed, to *d*-glucose, potassium bisulphate, and allyl isothiocyanate (p. 312).

A complex glycoside is **Solanine S.**,  $C_{54}H_{96}O_{18}N_2 \cdot H_2O$ , from *Solanum sodomacum*, as on hydrolysis it yields Solanidine S.,  $C_{18}H_{31}ON$ , *d*-glucose, *d*-galactose, and *d*-methyl-pentose.

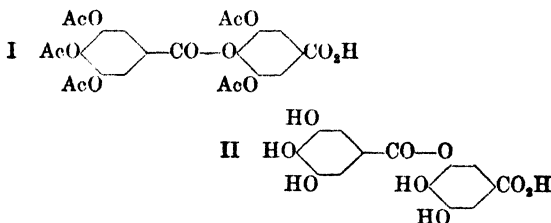
Some of the natural tannins are glycosides.

**Gallotannic acid**, derived from nut galls and one of the best-known tannins (p. 528), is a glycoside, and yields *d*-glucose and gallic acid in the molecular proportions 1 : 10 when hydrolysed with dilute mineral acids. The tannin of Chinese galls is a gallic acid derivative, and its structure, according to *Fischer*, is that of a penta-acylated glucose, the particular acyl group being the *m*-digalloyl group II, p. 949; it is therefore **pentadigalloyl-glucose**,  $C_6H_7O_6[CO \cdot C_6H_2(OH)_2 \cdot O \cdot CO \cdot C_6H_2(OH)_3]_5$ . Several products analogous in structure have been synthesized by *Fischer* and *Freudenberg* (B., 1912, 912, 2709), and have been shown to resemble natural tannin in many respects.

The first step in the synthesis consists in protecting the hydroxyl groups of gallic acid, either by acetylation or by conversion into its triethylcarbonato derivative,  $CO_2H \cdot C_6H_2(O \cdot CO_2Et)_3$ , by the aid of ethyl chloroformate,  $Cl \cdot CO_2Et$  (p. 316). The protected acid is next converted into the acid chloride,  $COCl \cdot C_6H_2(OAc)_3$  or  $COCl \cdot C_6H_2(O \cdot CO_2Et)_3$ , which can be condensed with *d*-glucose in the presence of an organic base, and by subsequent elimination of the acetyl or carbethoxy groups, by careful hydrolysis pentagalloyl-glucose is obtained. Galloyl derivatives of glycerol, erythritol and mannitol have been prepared by similar methods, and all have the

property of precipitating gelatine in much the same manner as tannin.

To introduce *p*-digalloyl groups into glucose the following series of reactions are carried out: Gallic acid  $\rightarrow$  triacetyl-gallic acid  $\rightarrow$  triacetyl-galloyl chloride. The latter is then condensed in the presence of dilute alkali with 3:5-diacetyl-gallic acid,  $\text{CO}_2\text{H}\cdot\text{C}_6\text{H}_2(\text{OH})(\text{OAc})_2$ , a product obtained by the partial hydrolysis of the triacetylated acid. By this condensation penta-acetyl-digallic acid (I) is obtained. This acid is



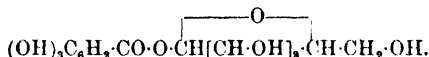
converted into its acid chloride by means of  $\text{PCl}_5$ , and the pentacetyldigalloyl chloride then condensed with *d*-glucose, and the acetyl groups removed from the final condensation product by hydrolysis with methyl alcohol and concentrated hydrochloric acid, or by means of a little sodium ethoxide, and  $\beta$ -pentadigalloylglucose is thus obtained. This closely resembles the tannin from Chinese galls, but has a slightly different optical rotation. They were also able to show that by methylating gallic acid, preparing pentamethyl-*p*-digalloyl chloride, and condensing this with glucose, a product is formed which is identical with the methyl tannin obtained by the action of diazomethane on natural Chinese tannin (B., 1913, 1116).

During the course of the work it was proved that when penta-acetyl-*p*-digallic acid (I) is hydrolysed the product is not the corresponding *p*-digallic acid but the isomeric *m*-digallic acid (II) (B., 1913, 1116; 1918, 45).

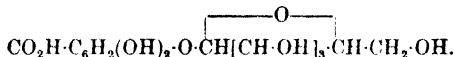
A simple glucogallic acid can be isolated from Turkish gall nuts; it is a condensation product derived from one molecule of glucose and one of gallic acid, and can be methylated. The methyl derivative has no reducing properties, and when hydrolysed by methyl alcoholic potash yields gallic acid trimethyl ether, and hence the conclusion is drawn that this natural product is formed by the condensation of the glucose



molecule with the carboxylic group of the gallic acid (*Feist* and *Haun*, Arch. Pharm., 1913, **251**, 468):



A synthetic product,  $\beta$ -glucisido-tannic acid, obtained by *Fischer* (B., 1912, 3773), is not identical, and probably has the ether constitution:



The products formed from hydroxy aromatic acids by the condensation of the COOH group of one molecule with the phenol group of a second are termed by *Fischer* **depsides**, and di-, tri-, and tetra-depsides can be obtained according to the number of molecules of acid thus condensed together to form a chain. Such depsides are esters derived from phenols, and, as such, can be hydrolysed.

Another group of natural glycosides is the **saponins** which are widely distributed in the vegetable kingdom. They are soluble in water, insoluble in ether, form emulsions with oils, and prevent the deposition of finely-divided particles. They have a bitter acrid taste and are characterized by giving a soapy foam when shaken with water, and by their toxic action on cold-blooded animals. When hydrolysed they yield a sugar or sugars and **sapogenins** (cf. Chap. LXII, F.).

All the natural and synthetic glucosides can be divided into two groups,  $\alpha$  and  $\beta$ , corresponding in structure with the two stereo-isomeric methylglycosides, and they are readily distinguished by their behaviour towards certain enzymes. Thus all  $\beta$ -glycosides—and practically all the natural glycosides belong to this group—are readily hydrolysed by water in the presence of emulsin (p. 947), whereas the  $\alpha$ -glycosides are hydrolysed by maltase, but not by emulsin. Within recent years numerous glycosides have been synthesized by means of enzymes. Compare Chap. LXIX, D3.

The common sugar present in natural glycosides is *d*-glucose, but *d*-galactose, rhamnose, and arabinose are also found. A convenient method for ascertaining the sugar present, when it is found difficult to isolate it, is to study the rates of hydrolysis of the glycoside in the presence of different sugars. Most of the sugars will have no influence on the rate of hydrolysis, but one

particular sugar will produce a retardation of the hydrolysis, and this may be accepted as the one present in combination in the particular glycoside.

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## LVII. TERPENES AND CAMPHORS \*

**Essential Oils.**—Many plants, especially varieties of *Coniferæ* and of *Citrus*, contain, in their leaves, blossoms and fruits, oily substances to which they owe their peculiar fragrance or odour, and which can be obtained from them by distillation in steam, by pressure, or by extraction with a low boiling solvent. These oils, "essential oils", were formerly grouped together in a special class, but now they are recognized as being more or less heterogeneous; thus oil of bitter almonds is benzoic aldehyde, and Roman oil of cumin is a mixture of cymene and cumic aldehyde, &c. Many of these ethereal oils contain unsaturated hydrocarbons, which are usually termed **terpenes**. The common hydrocarbons met with have the general formula  $C_{10}H_{16}$ , and are spoken of as terpenes proper; but, in addition to these, hydrocarbons, represented by the formula  $C_5H_8$  and known as **hemiterpenes**, exist. The commonest of these is **isoprene**, obtained by distilling caoutchouc. Hydrocarbons represented by the formula  $C_{15}H_{24}$  are termed **sesquiterpenes**, and the more complex hydrocarbons,  $(C_5H_8)_n$ , **polyterpenes**. Certain ethereal oils consist chiefly of such hydrocarbons, e.g. turpentine, oil of citron, orange oil, and oil of thyme. Other oils contain appreciable amounts of oxygenated compounds, mainly of an alcoholic, ketonic or ester character, e.g. camphor and menthone,  $C_{10}H_{16}O$ , pulegone, &c. Many of these terpenes and ketones are reduced benzene derivatives, e.g. limonene, menthone; others again are more complex ring compounds, e.g. pinene and camphor. In addition a third group is known, namely, open-chain olefinic hydrocarbons, alcohols, aldehydes, or ketones, e.g. citronellal, geraniol, linalool.

The terpenes are widely distributed in the vegetable kingdom, especially in the *Coniferæ* (*Pinus*, *Picea*, *Abies*, &c.), in

\* Simonsen, *The Terpenes*, Cambridge, 1931.

the varieties of Citrus, &c. The products which are isolated in the first instance from the individual plants, and which according to their source are designated terpene, citrene (from oil of citron), hesperidene (from oil of orange), thymene (from thyme), carvene (from oil of cummin), eucalyptene, olibene, &c., have for the most part the formula  $C_{10}H_{16}$ , and approximately equal boiling-points ( $160^{\circ}$ – $190^{\circ}$ ); they are not, however, chemical individuals, but mixtures of isomeric compounds.

With the exception of camphene they are all liquid, but it is hardly possible to separate them completely by fractional distillation. The terpenes can, however, be obtained chemically pure from crystalline derivatives, and numerous compounds belonging to this class have been synthesized.

For simplicity the terpenes and allied oxygen compounds (camphors) may be divided into the following groups:

- A. Open-chain olefinic compounds.
- B. Monocyclic terpenes.
- C. Dicyclic or bridged terpenes.
- D. Tricyclic terpenes.
- E. Irone and Ionones.
- F. Sesquiterpenes.
- G. Triterpenes.

Practically all the compounds dealt with in these seven divisions could have been discussed under the aliphatic and cyclic compounds. A clearer view, however, of their relationships is obtained by bringing them together under the general heading of terpenes and camphors.

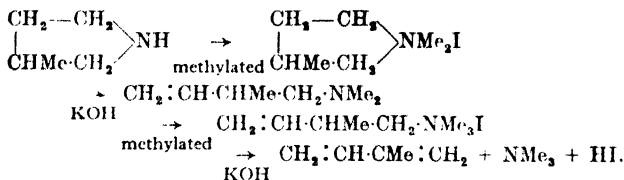
## A. Acyclic Olefinic Terpenes

### 1. HYDROCARBONS

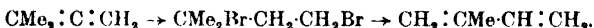
**Isoprene**, the best-known hemiterpene, is a diolefine represented by the constitutional formula,  $CH_2:CMc:CH:CH_2$ , 2-methyl- $\Delta^{1:3}$ -butadiene. It is a colourless liquid, b.-pt.  $37^{\circ}$ , formed by the dry distillation of rubber, or by decomposing turpentine at a dull red heat (cf. *Staudinger*, B., 1911, 2212). When boiled with an alcoholic solution of HCl it is converted into its isomeride dimethylallene  $(CH_3)_2C:C:CH_2$ . At  $300^{\circ}$  it undergoes polymerization to di-isoprene (probably dipentene), and is transformed into products analogous to rubber when

treated with concentrated hydrochloric acid or metallic sodium, when kept for some time or when exposed to sunlight in the presence of traces of acid. Three syntheses of isoprene are of interest.

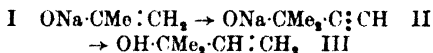
(a) From 3-methyl-pyrrolidine by exhaustive methylation, p. 999 (*Euler, J. pr., [ii], 57, 132*):



(b) From dimethyl-allene by the addition of two molecules of hydrogen bromide and subsequent elimination of the same (*Ipatieff, ibid. 55, 4*):



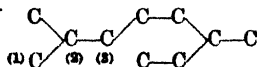
(c) The sodium derivative of acetone I, obtained by the action of sodamide, reacts with acetylene yielding compound II, which on reduction gives III, from which isoprene is formed by the elimination of water (D. R. P.).



All three types of natural terpenes may be regarded as built up of isoprene units.

Within recent years isoprene and butadiene derivatives generally have received marked attention on account of their relationships to synthetic rubbers (Chap. LXI, E.).

Most of the natural acyclic compounds contain the skeleton



with an olefine link between 1 and 2 or 2 and 3, and contain oxygen either as alcohols or aldehydes.

Two acyclic hydrocarbons,  $\text{C}_{10}\text{H}_{16}$ , are obtained from natural sources: (I) **Myrcene**, 2-methyl-6-methene- $\Delta^{3:7}$ -octadiene,  $\text{CH}_3\cdot\text{CMe}:\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{C}(\text{CH}_3):\text{CH}:\text{CH}_2$ , from oil of bay (*Myrcia acris*) and verbena oil (leaves of *Lippia citriodora*); (II) **Ocimene**, 2:6-dimethyl- $\Delta^{1:3:7}$ -octatriene,  $\text{CH}_3:\text{CMe}\cdot\text{CH}_2\cdot$

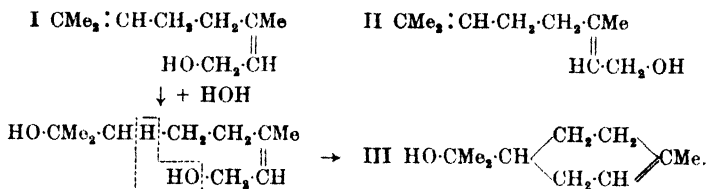
$\text{CH}_2\cdot\text{CH}\cdot\text{CMe}\cdot\text{CH}\cdot\text{CH}_2$ , from the leaves of *Ocimum basilicum*. Both hydrocarbons give the same dihydro derivative, dihydro-myrcene, which yields a **tetrabromide** melting at  $87^\circ\text{--}88^\circ$ . The fact that both hydrocarbons on reduction with sodium and alcohol take up only two atoms of hydrogen and on bromination only four atoms of bromine indicates that two of the olefine links are conjugate and the formulæ given above are based on the results of ozonolysis. Myrcene ozonide after decomposition and subsequent oxidation with hypobromite gives succinic acid, whereas ocimene on ozonolysis gives acetic and malonic acids and methylglyoxal.

## 2. ALCOHOLS

**Geraniol**,  $\text{C}_{10}\text{H}_{18}\text{O}$ ,  $\text{CH}_2\cdot\text{CMe}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}\cdot\text{CH}\cdot\text{CH}_2\text{OH}$  (I), 2:6-dimethyl- $\Delta^{1:6}$ -octadiene-8-ol or  $\text{CH}_3\cdot\text{CMe}\cdot\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}\cdot\text{CH}\cdot\text{CH}_2\cdot\text{OH}$  (II), 2:6-dimethyl- $\Delta^{2:6}$ -octadiene-8-ol, the alcohol corresponding with  $\alpha$ -citral, is found in the oil from the grass *Cymbopogon Martinii* (var. *motia*) common in India, and is also present either free or as esters in many other oils. It has b.-pt.  $229^\circ\text{--}230^\circ$ , yields a **diphenylurethane**, m.-pt.  $82^\circ$ , a **tetrabromide**, m.-pt.  $70^\circ\text{--}71^\circ$ , and a stable compound  $\text{C}_{10}\text{H}_{18}\text{O}$ ,  $2\text{NaHSO}_3$ . Its structure follows from its relationship to  $\alpha$ -citral, and also from a study of the products formed by the oxidation with dichromate and sulphuric acid of the polyhydroxy compound formed by the action of cold permanganate on the alcohol. These are lævulic and oxalic acids and point to formula (II) (*Blumann and Zeitschel*, 1911). On the other hand, *Kötz and Steche* (1924) by carefully oxidizing geraniol itself or its mono- or di-oxide with dilute permanganate obtained an acid  $\boxed{\text{CO}_2\text{H}}\cdot\boxed{\text{CMe}(\text{OH})}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$ , which immediately lost formic acid (dotted lines), and thus supports formula (I). In all probability geraniol is a mixture of I and II, and the oils from different sources contain different amounts of the two (cf. *Grignard* and others, *Bull. Soc.*, 1925, iv, **37**, 542; 1927, **41**, 999; 1928, **43**, 1091, 1212).

**Nerol**,  $\text{C}_{10}\text{H}_{18}\text{O}$  (1902), stereo-isomeric with geraniol, is present in oil of bergamot, neroli oil, &c. It has b.-pt.  $225^\circ\text{--}226^\circ$ , yields a **diphenylurethane**, m.-pt.  $52^\circ\text{--}53^\circ$ , a **tetrabromide**, m.-pt.  $116^\circ\text{--}118^\circ$ , and has an odour quite different from that of

geraniol. Unlike the latter it forms no compound with calcium chloride, and the two alcohols may be separated by means of this reagent. Both alcohols are hydrated by dilute sulphuric acid, yielding  $\alpha$ -terpineol (terpin hydrate III), but as nerol reacts much more readily than geraniol, it is regarded as having the *trans* structure and geraniol as the *cis* stereoisomeride (II).

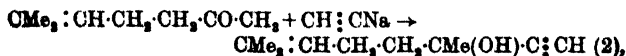


It is probable that nerol is a mixture of *trans* 2 : 6-dimethyl- $\Delta^{2:6}$ -octadiene-8-ol with a small amount of the *trans* form of the  $\Delta^{1:6}$ -isomeride.

**Linalool or Coriandrol** (1853) is again probably a mixture of two components, viz. 2 : 6-dimethyl- $\Delta^{2:7}$ -octadiene-6-ol,  $\text{CH}_3\cdot\text{CMe}\text{:CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe(OH)}\cdot\text{CH}\text{:CH}_2$ , and 2 : 6-dimethyl- $\Delta^{1:7}$ -octadiene-6-ol,  $\text{CH}_3\text{:CMe}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe(OH)}\cdot\text{CH}\text{:CH}_2$ . It is found in oil of linaloe obtained from the wood of *Ocotea caudata* (*Licari kanali*) from Mexico and French Guiana. It is optically active as it contains a centre of dissymmetry, viz. the C atom to which Me and OH are attached. The *l* form also occurs in rose oil, bergamot oil and the *d* form in coriander oil and orange oil. It is labile and shows a tendency to isomerize to geraniol, e.g. by treatment with acetic anhydride and subsequent hydrolysis, hence oxidation with *acid* oxidizing agents gives rise to the same products as are obtained from geraniol, and for some years it was thought to be a primary alcohol stereo-isomeric with geraniol.

It is stable towards alkalis, and in this respect differs from geraniol which yields 2-methyl- $\Delta^2$ -hepten-6-ol,  $\text{CMe}_2\text{:CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH(OH)}\cdot\text{CH}_3$ . As a tertiary alcohol it has a relatively low b.-pt., 198°–199°, and  $[\alpha]_D - 20^\circ$ . Its phenylurethane has m.-pt. 63°–65°.

It has been synthesized by *Ruzicka* and *Fornasir* (Helv., 1919, 182) by the condensation of 2-methyl- $\Delta^2$ -hepten-6-one (1) and sodium acetylide to product (2),



which on reduction in moist ethereal solution with sodium gave *dl*-linalool. Both the natural and the synthetic products are probably mixtures of the  $\Delta^{2:7}$ -compound with small amounts of the isomeric  $\Delta^{1:7}$ -compound (cf. p. 955).

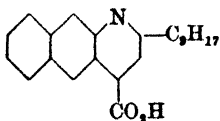
Geraniol can be converted into linalool by first forming geranyl chloride by the action of hydrogen chloride in toluene solution at  $100^\circ$  and treatment of the chloride with moist silver oxide.

Myrcene (p. 953) is formed when linalool is catalytically reduced by *Sabatier-Senderens'* method at  $135^\circ$ – $140^\circ$  or by distilling the alcohol with a little iodine.

### 3. ALDEHYDES

**Citronellal, Rhodinal** (1872),  $C_{10}H_{18}O$ , is the aldehyde corresponding with citronellol. It yields the latter on reduction, and an acid, citronellic acid,  $C_{10}H_{18}O_2$ , on oxidation. It is probably a mixture of the two isomers, viz. 2 : 6-dimethyl- $\Delta^2$ -octen-8-al and 2 : 6-dimethyl- $\Delta^1$ -octen-8-al, corresponding with the two citronellois.

It is present in citronella oil from the grass *Cymbopogon nardus* of Ceylon, also in the oil from certain species of *Eucalyptus*. It has b.-pt.  $205^\circ$ – $206^\circ$ ,  $[\alpha]_D + 12.3^\circ$ , forms a **semi-carbazone**, m.-pt.  $82.5^\circ$ , and with  $\beta$ -naphthylamine and pyruvic acid **citronellyl- $\beta$ -naphthocinchoninic acid**, m.-pt.  $225^\circ$ ,

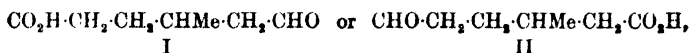


Like most aliphatic aldehydes it forms acetals by the action of hydrogen chloride on its alcoholic solutions.

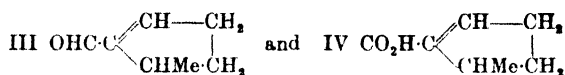
The dual character of the aldehyde was proved by *Harries* (A., 1915, 410, 8) by careful examination of the products formed by the ozonolysis of citronellal-dimethylacetal. Among these products were formic acid, a peroxide of 6-methyloctan-2-one-8-al,  $CH_3 \cdot C(O_2) \cdot CH_2 \cdot CH_2 \cdot CH_3 \cdot CHMe \cdot CH_2 \cdot CHO$ , and the

cyclic ketone,  $CH_3 \cdot CO \cdot C \begin{array}{l} \nearrow CH \cdot CH_2 \\ \searrow CH_2 \cdot CH_2 \end{array} \rangle CH \cdot CH_3$ , formed by the cyclization of the ketone formed from the peroxide. These

products point to the  $\Delta^1$ -structure of the original aldehyde. On the other hand, the isolation of acetone (as peroxide), the semialdehyde of  $\beta$ -methyladipic acid (I or II), methyl- $\Delta^1$ -cyclopenten-1-al (III), and methyl- $\Delta^1$ -cyclopentene-1-carboxylic acid (IV) all point to the  $\Delta^2$ -structure, as the two semialdehydes can be regarded as formed from a primary oxidation product,  $\text{CHO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CHO}$ , which gives

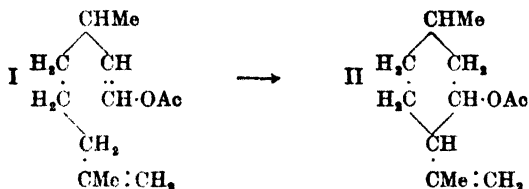


and these on cyclization give



With sodium bisulphite citronellal gives rise to 3 distinct additive compounds: (1) Addition to the aldehyde group; (2) Addition to the olefine link,  $\text{CH}_3\cdot\text{CMe}(\text{SO}_3\text{Na})\cdot\text{CH}_2$ , and (3) addition to both CHO and C:C (cf. *Tiemann*, B., 1898, 3306; 1899, 812).

Citronellal is a labile compound and, in addition to readily undergoing oxidation, forms ring compounds with great ease. Thus with acetic anhydride it forms *isopulegyl acetate* II, and this on hydrolysis gives *isopulegol*. The aldehyde reacts with the anhydride, giving the acetate of the enolic form I, which on cyclization gives the *isopulegyl acetate* (*Tiemann* and *Schmidt*, B., 1896, 913; 1897, 27).

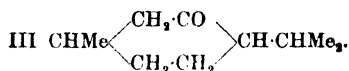


The  $\Delta^2$  form of the aldehyde can also react, but a shift of the double bond would occur during the reaction.

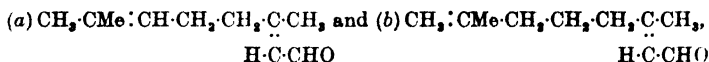
The yield of citronellal obtained by oxidizing citronellol with chromic acid is poor owing to the readiness with which the aldehyde forms cyclic compounds; among these are *isopulegole* and *menthone* III—the latter can be regarded as formed by the addition of  $\text{H}_2\text{O}$  to the  $\Delta^2$  double link (OH to



C and H to CH) and the closing of the ring by the elimination of water (OH from CH·OH and H from ·CHO).



**Citral**,  $\text{C}_{10}\text{H}_{16}\text{O}$ , is the commonest acyclic aldehyde and constitutes about 80 per cent of lemon grass oil (*Cymbopogon flexuosus*) and occurs in oil of lemons and oil of oranges. The natural oil contains two components,  $\alpha$ -citral or geranial and  $\beta$ -citral or neral. The former is the aldehyde corresponding with geraniol and is probably a mixture of the 2:6-dimethyl- $\Delta^{2:6}$ -octadien-8-al (a) with the isomeric  $\Delta^{1:6}$ -compound (b), viz.



whereas neral is a mixture of the two stereo-isomeric *trans*-compounds corresponding with nerol (cf., however, Verley, Bull. Soc., 1928, iv, 43, 854).

Geranial can be obtained by the gentle oxidation of geraniol with ammonia and silver oxide, and the aldehyde, b.-pt.  $153^\circ/13$  mm., on further oxidation, gives geranic acid,  $\text{C}_{10}\text{H}_{16}\text{O}_2$ .

Citral, from lemon grass oil, consists of nearly 90 per cent of (a) and only 10 per cent of (b). The  $\alpha$ -citral is most readily isolated as its sparingly soluble sodium bisulphite compound, whereas the  $\beta$ -compound is most readily separated from the mixture by means of its condensation product with cyano-acetic acid, as the  $\beta$ -aldehyde reacts much more readily than its  $\alpha$ -isomer with this reagent. The  $\beta$ -compound can also be obtained by the cautious oxidation of nerol.

$\alpha$ -Citral has b.-pt.  $118^\circ\text{--}119^\circ/12$  mm., and the  $\beta$ -citral, b.-pt.  $117^\circ\text{--}118^\circ/20$  mm., and both have very high molecular refractions due to the presence of the conjugated linkages (C:C and C:O). They are colourless oils which rapidly turn yellow on exposure to the air. The more important crystalline derivatives are semicarbazones,  $\alpha$ -needles, m.-pt.  $164^\circ$ , and  $\beta$ -leaflets, m.-pt.  $171^\circ$ , citrylidene cyano-acetic acids,  $\alpha$ , m.-pt.  $122^\circ$ , and  $\beta$ ,  $94^\circ$ .

The structure of  $\alpha$ -citral as the  $\Delta^{2:6}$ -compound follows from its formation from geraniol and also from a study of the

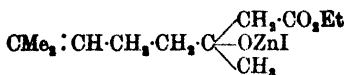
products formed by careful oxidation with permanganate followed by dichromate and acid. The products are acetone, lævulic and oxalic acids (*Tiemann and Temmler*, B., 1895, 2132).

Support is also afforded by the formation of 2-methyl- $\Delta^2$ -heptene-6-one,  $\text{CH}_3\cdot\text{CMe}:\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_3$ , and acetaldehyde by digesting the  $\alpha$ -compound with alkali (*Bull. Soc.*, 1897, iii, 17, 175). The products of ozonolysis (*Harries*, B., 1903, 1933; 1907, 2823), viz. acetone, lævulaldehyde and glyoxal, also point to the  $\Delta^{2:6}$ -structure, but the presence of small amounts of formaldehyde points to the  $\Delta^{1:6}$ -structure, and a careful comparison of the amounts of acetone and formaldehyde indicates the presence of some 93 per cent of the  $\Delta^{2:6}$ -compound in ordinary  $\alpha$ -cital (*Bull. Soc.*, 1924, iv, 35, 932).

The products formed by the catalytic hydrogenation of citral vary with the catalyst, the temperature and the pressure. With a nickel catalyst at  $190^\circ$  and low pressures the product is *dl*-citronellal formed by the addition of hydrogen to the  $\Delta^6$  olefine link. At moderate pressures the product is the saturated alcohol, 2:6-dimethyloctan-8-ol, and at still higher pressure the saturated alcohol together with the saturated hydrocarbon, 2:6-dimethyloctane. By using a palladium catalyst the only product is the hydrocarbon.

Geranic acid has been synthesized and as citral is formed by distilling calcium geranate and formates, and geraniol and citronellal and citronellol can be obtained from citral, the syntheses of all these compounds have been accomplished.

*Barbier and Bouveault's* synthesis (*C. R.*, 1896, 122, 393) is as follows. 2-Methyl- $\Delta^2$ -hepten-6-one reacts with metallic zinc and ethyl iodoacetate (*Reformatsky* reaction), yielding the compound:



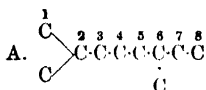
With dilute acid this yields the hydroxy ester:



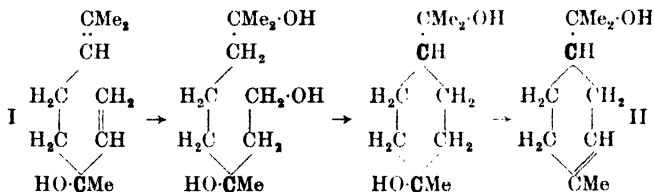
and when this is distilled with acetic anhydride, water is eliminated and ethyl geranate,  $\text{CMe}_2:\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}:\text{CH}\cdot\text{CO}_2\text{Et}$ , formed.

## 4. RING FORMATION

Acyclic compounds of the types described, viz. with the skeleton A, exhibit a great tendency to form cyclic compounds:

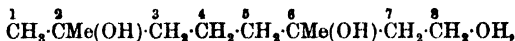


One of the most interesting of such changes is the conversion of *l*-linalool I into *d*-terpineol II as the centres of dissymmetry in the two molecules are different as shown by the heavy type of the centres in the following scheme:



The above ring closure occurs between carbons numbered 3 and 8, and numerous similar ring closures take place readily: (a) Thus *α*-citral on dehydration with dilute sulphuric acid yields *p*-cymene, *p*-methylisopropylbenzene; (b) isopulegyl acetate is formed from the acetate of the enolic form of citronellal (p. 956); (c) the formation of terpineol from geraniol. In all these cases the products are benzene or reduced benzene derivatives with a six-carbon ring.

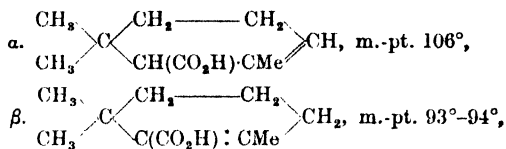
The trihydroxy alcohol,



is probably first formed, and ring closure takes place by the elimination of H attached to C No. 3 with OH attached to C No. 8.

Another type of ring closure which is very common is by the union of carbon atoms numbered 2 and 7, under the influence of moderately concentrated sulphuric acid. Thus geraniolene, dihydromyrcene, geraniol, citral and geranic acid all yield ring compounds by union of carbon atoms 2 and 7. The ring is a 6-membered carbon ring, and the CH<sub>2</sub>OH, CHO or CO<sub>2</sub>H groups remain intact. In nearly all cases the product is a

mixture of two isomeric compounds differing in the positions of the olefine link in the ring; thus  $\alpha$ - and  $\beta$ -cyclogeranic acids obtained by the action of 70 per cent sulphuric acid or geranic acid (p. 958) are represented by the following formulæ:



i.e. 2 : 6 : 6-trimethyl- $\Delta^2$ -cyclohexene-1-carboxylic acid and the isomeric  $\Delta^1$ -compound.

## B. Monocyclic Terpenes and Camphors

### 1. TERPENES

Many of the compounds are to be regarded as hydrogenated derivatives of cymene (p. 412). Their close relationship to cymene can be shown in very different ways: e.g. (a) the hydrocarbon **terpinene** when heated with iodine is transformed into *p*-cymene, i.e. *p*-methyl-isopropyl-benzene; (b) the ketone **carvone** when heated with mineral acids yields carvacrol, i.e. 1-methyl-2-hydroxy-4-isopropyl-benzene (p. 483); (c) on oxidation many terpenes yield terephthalic acid; (d) by the addition of bromine and subsequent elimination of HBr many monocyclic terpenes yield benzene hydrocarbons (B., 1898, 2068); (e) heating with sulphur usually removes the excess hydrogen as hydrogen sulphide and a substituted benzene hydrocarbon, usually cymene, is formed (Vesterberg, B., 1903, 4200).

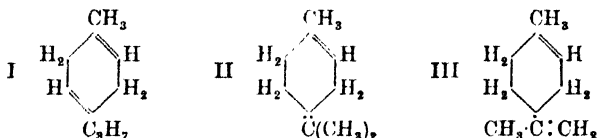
The unsaturated nature of these compounds follows from the readiness with which they form additive compounds; they yield **dihydrochlorides**,  $\text{C}_{10}\text{H}_{18}\text{Cl}_2$ , **tetrabromides**,  $\text{C}_{10}\text{H}_{16}\text{Br}_4$ , **nitroso-chlorides**,  $\text{C}_{10}\text{H}_{16}(\text{NOCl})_2$ , **nitrosites**,  $\text{C}_{10}\text{H}_{16}(\text{NO})(\text{NO}_2)$ , and **nitrosates**,  $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_4$ . These compounds are of considerable importance, as most of them are well-defined crystalline compounds with definite melting-points, and can therefore be made use of in separating and identifying the various liquid terpenes. The nitroso-chlorides were first prepared by Tilden (J. C. S., 1877, 554), by the direct action of nitrosyl

chloride, but are now usually obtained by *Wallach's* method, viz. by the action of a mixture of ethyl nitrite, acetic and hydrochloric acids on the hydrocarbon. The nitrosites are usually obtained by the action of sodium nitrite and acetic acid on the hydrocarbon, and the nitrosates by the direct addition of nitric peroxide or by the action of amyl nitrite and concentrated nitric acid. An interesting group of compounds are the **nitrolamines**, obtained by the action of amines (piperidine or benzylamine) on the nitroso-chlorides. They contain the NHR group in place of the chlorine of the nitroso-chlorides. Such compounds crystallize well, and can be used for identifying the various terpenes.

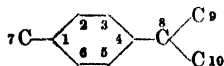
All these reactions point to the presence (a) of a six-membered carbon ring in the monocyclic terpenes; (b) to the presence of two side chains, usually in *p*-positions, one consisting of the CH<sub>3</sub> group, and the second containing the grouping



; (c) to the presence of two double bonds in the molecule. These may be both in the carbon ring, or one in the ring and one in a side chain, e.g.:



Fourteen such isomerides are theoretically possible. The carbon atoms are usually numbered as follows:



The saturated compound C<sub>10</sub>H<sub>20</sub>, viz. *p*-methyl-isopropyl-cyclohexane, is called **menthane**,\* and the compounds C<sub>10</sub>H<sub>16</sub> are **menthadienes**. I is Δ-1:4-menthadiene, II is Δ-1:4 (8)-menthadiene, and III Δ-1:8 (9)-menthadiene.

The double linking in No. II between a carbon atom in the ring and a carbon of a side chain is termed a **semicyclic linking**. Such an unsaturated linking is quite stable under the influence of heat, but in the presence of acids it wanders into

\* The name **terpane** is sometimes used for this hydrocarbon and terpadienes for the menthadienes.

the nucleus, e.g.  $\Delta^{4(8)}$ -*p*-menthene is readily transformed into  $\Delta^3$ -*p*-menthene.

A few of the terpenes contain the methyl- and isopropyl-groups in the meta-positions, e.g. sylvestrene; such compounds are termed *m*-menthadienes.

The nitroso-chlorides are frequently colourless, and then appear to be bimolecular; some give blue solutions containing the monomolecular form. Compounds with a semicyclic linking  $>\text{C}:\text{CR}_2$  yield unimolecular blue nitroso-chlorides volatile with steam. The blue compounds are true nitroso-compounds. When the NO group becomes attached to  $>\text{CH}$  it usually passes over into the isonitro-group  $>\text{C}:\text{N}\cdot\text{OH}$ , and the compound becomes colourless.

The following hydrocarbons belong to this group:

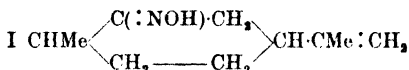
*d*- and *l*-**Limonene** and **Dipentene** (*dl*-limonene) have been shown to be  $\Delta^{1:8(9)}$ -menthadienes (Formula III, p. 962). *d*-Limonene is also known under the names *hesperidene*, *citrene* and *carvene*, and is the chief constituent of oil of dill and oil of erigeron, and oil of citron consists mainly of *d*-limonene and pinene. The *l*-isomer occurs with *l*-pinene in the oil from silver-fir cones. They have b.-pt.  $176^\circ$  and  $[\alpha]_D \pm 126$ , but the rotation varies with different samples due to the presence of smaller or larger amounts of the racemic isomer. Dipentene occurs with cineole in *Oleum cinæ*, and is formed when other terpenes, e.g. pinene, camphene or sylvestrene are heated at  $250^\circ$ – $270^\circ$  for several hours, and is therefore one of the most stable terpenes. It may also be obtained by polymerizing isoprene, by the elimination of water from  $\alpha$ -terpineol or by distilling caoutchouc.

Among the derivatives are the following:

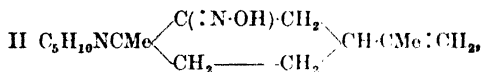
By the addition of HCl or HBr in the absence of moisture **monohydro-chlorides** or **-bromides** are formed as oils, and these correspond in structure with  $\alpha$ -terpineol. In the presence of moisture the product is a **dihydrochloride**,  $\text{C}_{10}\text{H}_{18}\text{Cl}_2$ , m.-pt.  $49^\circ$ – $50^\circ$ , and with the two chlorine atoms in positions 1 and 8 as on treatment with dilute alkali it yields dipentene,  $\alpha$ -terpineol and *cis* and *trans* terpin (p. 971). The dihydrochloride is isomeric with the compound, m.-pt.  $25^\circ$ , obtained by the action of HCl on cineole.

*d*- and *l*-Limonenes yield optically active **tetrabromides**, m.-pt.  $104^\circ$ – $105^\circ$  and  $[\alpha]_D \pm 73^\circ$ , whereas **dipentene tetrabromide** is inactive and melts at  $125^\circ$ . Each limone forms two nitroso-

chlorides  $\alpha$  and  $\beta$ ; those from the active hydrocarbons melt respectively at  $103^{\circ}$ – $104^{\circ}$  and  $105^{\circ}$ – $106^{\circ}$  and have  $[\alpha]_D \pm 314^{\circ}$  and  $\pm 241^{\circ}$ ; dipentene  $\alpha$ -nitroso-chloride is inactive and has m.-pt.  $78^{\circ}$ . These nitroso-chlorides are bimolecular (*Baeyer*, B., 1895, 652; *Leach*, J. C. S., 1905, 413), and the  $\alpha$  and  $\beta$  forms are probably stereo-isomeric. They react with alkali, yielding carvoxime I,



(p. 972), and with piperidine 6-nitrolpiperidines II,

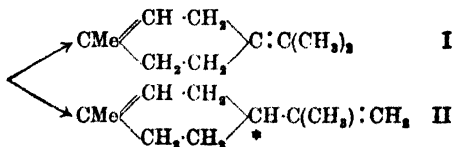
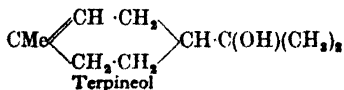


are formed. The  $\alpha$ -*d*- and  $\alpha$ -*l*- have m.-pt.  $93^{\circ}$ – $94^{\circ}$  and  $[\alpha]_D \pm 67.5^{\circ}$ , the  $\beta$ -*d*- and  $\beta$ -*l*- m.-pt.  $110^{\circ}$ – $111^{\circ}$  and  $[\alpha]_D \pm 60^{\circ}$ , and the  $\alpha$ - and  $\beta$ -dipentene compounds melt at  $154^{\circ}$  and  $152^{\circ}$ , and are inactive.

**Limone nitrosate** has a low melting-point and **dipentene nitrosate** melts at  $84^{\circ}$ .

By catalytic hydrogenation with nickel at  $180^{\circ}$  the limonenes yield *p*-menthane, but with copper at the same temperature  $\Delta^1$ -*p*-menthene. Warming with mineral acids produces conversion into terpinene ( $\Delta^{1:8}$ -menthadiene) with a little *p*-cymene.

Various structures have been given to the limonenes from time to time. Their structure as  $\Delta^{1:8(9)}$ -menthadienes is based on their close relationships to  $\alpha$ -terpineol and carvone, the constitutions of which have been confirmed by synthesis. Thus  $\alpha$ -terpineol on dehydration yields dipentene, and the latter when shaken with a dilute solution of sulphuric acid in acetic acid yields  $\alpha$ -terpineol. If molecular rearrangements do not occur during these reactions, it is clear that dipentene must have a constitutional formula corresponding with I or II.

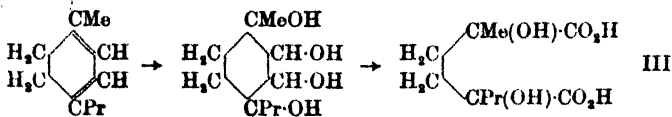


Formula I is not dissymmetric, and therefore cannot represent the molecules of *d*- and *l*-limonenes and of dipentene; formula II, on the other hand, contains an asymmetric carbon atom, the one indicated by an asterisk, the molecule is dissymmetric, and can form *d*-, *l*-, and *r*-modifications.

The correctness of formula II is confirmed by a study of some of the reactions of dipentene.

Dipentene forms a nitroso-chloride (colourless), and this with alkalis gives the oxime of carvone,  $\cdot\text{CH}(\text{NO})\cdot \rightarrow \cdot\text{C}(\text{N}\cdot\text{OH})\cdot \rightarrow \cdot\text{CO}\cdot$  (p. 972). The oxime when hydrolysed yields carvone, and this on reduction yields dihydrocarveol, a secondary alcohol formed by the addition of two atoms of hydrogen to one of the ethylene linkings and two atoms of hydrogen to the carbonyl group. Dihydrocarveol when oxidized yields a ketonic alcohol,  $\text{CH}_3\cdot\text{C}_6\text{H}_9(\text{OH})\cdot\text{CO}\cdot\text{CH}_3$ , proving the presence of the  $\cdot\text{C}(\text{CH}_3):\text{CH}_2$  group in dihydrocarveol, carvone, and dipentene. The fact that the molecular refraction of limonene is normal and shows no exaltation agrees with the structure given, as the double links are not conjugated and neither is a semicyclic link.

**Terpinenes.**—The three terpinenes known as  $\alpha$ ,  $\beta$ , and  $\gamma$  are respectively  $\Delta^{1:3}$ ,  $\Delta^{1(7):3}$  and  $\Delta^{1:4}$ -*p*-menthadienes. All three compounds yield the same dihydrochloride which has been proved to be 1:4-dichloro-*p*-menthane, m.-pt.  $51^\circ$ – $52^\circ$ , and the corresponding dihydrobromide has m.-pt.  $58^\circ$ – $59^\circ$ . Not one of the three has been obtained in a pure state. The  $\alpha$ -compound from various oils or prepared in the laboratory by treating linalool or geraniol with concentrated formic acid, or by warming  $\alpha$ -phellandrene or dipentene with dilute sulphuric acid, always contains a certain amount of the  $\gamma$ -isomer. The  $\alpha$ -compound is characterized by forming a crystalline *nitrosite*, m.-pt.  $155^\circ$ , whereas the  $\gamma$ -compound gives a *nitroso-chloride*, m.-pt.  $111^\circ$ , and a *nitrosate*, m.-pt.  $116^\circ$ . When oxidized with permanganate the  $\alpha$ -compound yields 1-methyl-4-isopropyl-1:4-dihydroxy adipic acid III:



The dihydrochloride on treatment with alkali gives a glycol containing two tertiary hydroxyl groups as it yields an an-



hydride (a cineole), and as this differs from the cineole from 1 : 8-terpin it must be a 1 : 4-cineole, a structure confirmed by Wallach (A., 1906, **350**, 157; 1907, **356**, 200).

$\beta$ -Terpinene does not occur naturally, but the  $\gamma$ -compound is found—usually with the  $\alpha$ -isomer—in many oils, particularly coriander oil, oil of cumin, and ajowan oil. After removal of thymol from the latter the terpene fraction—thymene oil—is rich in the  $\gamma$ -compound, which yields 1 : 2 : 4 : 5-tetrahydroxy-*p*-menthane on oxidation.

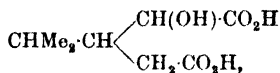
**Terpinolene**,  $\Delta^{1:4(6)}$ -menthadiene (Formula I, p. 962), is present in small amounts in certain oils and is formed when terpineol is boiled for a short time with formic acid or oxalic acid solution. It boils at 183°–185°, and is readily transformed by acids into terpinene. It forms a blue nitroso-chloride, and a tetrabromide, 1 : 2 : 4 : 8-tetrabromo-*p*-menthane, m.-pt. 118°, and a dibromide, 4 : 8-dibromo- $\Delta^1$ -*p*-menthene, m.-pt. 69°–70°. The tetrabromide with alkali yields *p*-cymene, and with dilute permanganate it gives 1 : 2 : 4 : 8-tetrahydroxy-menthane, m.-pt. 148°–149°.

*d*- and *l*-**Silvestrenes** and the racemic form known as **Carvestrene** are  $\Delta^{1:8(9)}$ -*m*-menthadienes. The *d*-compound, b.-pt. 175°, is the chief dextro-rotatory constituent of Swedish and Russian oil of turpentine. It is one of the most stable of the terpenes, and gives a magnificent blue coloration with acetic anhydride and concentrated sulphuric acid. The  $\text{CH}_3$  and  $\text{C}_3\text{H}_5$  substituents are in the *m*-positions, as treatment with bromine and alkali converts it into *m*-cymene.

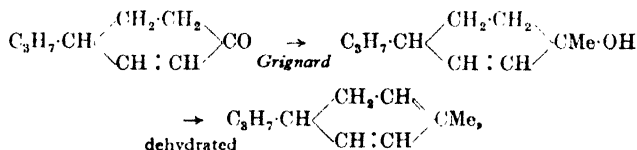
It has been synthesized from *m*-hydroxy-benzoic acid by Perkin and Tattersall (J. C. S., 1907, 480) by reducing to its hexahydro derivative, oxidizing to  $\gamma$ -ketohexahydrobenzoic acid, and proceeding as in the synthesis of terpineol.

**Phellandrenes**.—Three isomeric phellandrenes exist in nature: *d*- $\alpha$ -phellandrene in oil of bitter fennel, in elemi oil, ginger grass oil and in cinnamon oil, *l*- $\alpha$ -phellandrene in Australian eucalyptus oil (*Eucalyptus dives* and *E. phellandra*), and *d*- $\beta$ -phellandrene in water dropwort (*Phellandrium aquaticum*). The *d*- and *l*- $\alpha$ -phellandrenes are optical antipodes, and are both  $\Delta^{1:5}$ -menthadienes. The b.-pt. is 58°–59°/16 mm., and  $[\alpha]_D \pm 112^\circ$ . It is transformed into terpinene by the action of acids, and its dibromide with alkalis yields cymene. This constitution follows from the fact that nitro- $\alpha$ -phellandrene, when carefully reduced, yields active carvotanacetone,  $\Delta^5$ .

menthen-2-one, and has been confirmed (a) by a study of the products of oxidation (*Semmler*, B., 1903, 1749), the chief of which is the lactone of 1- $\alpha$ -hydroxy- $\beta$ -isopropylglutaric acid,



and (b) by the synthesis of  $\alpha$ -phellandrene from 4-isopropyl- $\Delta^2$ -hexen-1-one (A., 359, 285):

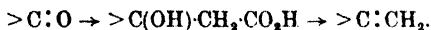


and also by its synthesis from carvone (p. 972).

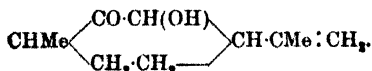
Carvone  $\xrightarrow{\text{HBr}}$  carvone hydrobromide  $\xrightarrow{\text{reduced}}$   $\Delta^6$ -menthen-2-one  $\xrightarrow{\text{PCl}_5}$  6-chloro- $\Delta^{1:6}$ -menthadiene  $\xrightarrow{\text{reduced}}$   $\alpha$ -phellandrene.

$\beta$ -Phellandrene is  $\Delta^{1(7):2}$ -menthadiene. It has boiling-point  $57^\circ/11$  mm.,  $[\alpha]_D + 65^\circ$ , and yields two nitrosites, melting-points  $97^\circ$  and  $102^\circ$ . Unlike the  $\alpha$ -isomer which yields an oily nitroso-chloride it yields two solid nitroso-chlorides, m.-pt.  $100^\circ$  and  $102^\circ$ , but with different rotations. Its constitution is based on the fact that it is oxidized by atmospheric oxygen to 4-isopropyl- $\Delta^2$ -hexen-1-one (A., 343, 29), and on its synthesis from carvone (J. pr., 72, 193; 75, 141).

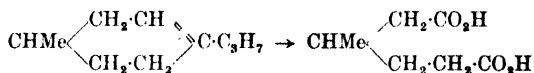
Carvone  $\xrightarrow{\text{reduced}}$  carvomenthol (menthan-2-ol)  $\xrightarrow{\text{dehydrated}}$   $\Delta^1$ -menthene  $\xrightarrow{\text{bromine}}$  terpenedibromide  $\xrightarrow{\text{alc. potash}}$   $\beta$ -phellandrene, or from 4-isopropyl- $\Delta^2$ -cyclohexen-1-one by condensing with ethyl bromoacetate and zinc, and finally eliminating  $\text{CO}_2$  and  $\text{H}_2\text{O}$ .



1- $\Delta^{2:8(9)}$ -*p*-Menthadiene is present in chenopodium oil. It forms a tetrabromide, m.-pt.  $117^\circ$ , viz. 2 : 3 : 8 : 9-tetrabromo-*p*-menthane, which is inactive. Its structure follows from the product of oxidation, viz. the  $\alpha$ -hydroxy-ketone,



**Menthene**, obtained from menthol by the elimination of water, is  $\Delta^3$ -menthene; when oxidized it yields a glycol, which on further oxidation gives  $\beta$ -methyladipic acid:



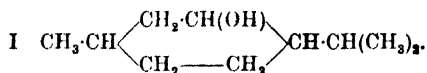
It has been synthesized by *Wallach* (B., 1906, 2504) by condensing 1-methylcyclohexan-4-one with ethyl  $\alpha$ -bromoisobutyrate and zinc, hydrolysing and eliminating  $\text{CO}_2$  and water.

A synthetical **terpene** or **dihydro-cymene** boiling at  $174^\circ$  has been prepared from succinylsuccinic ester (pp. 403, 539) (B., 1893, 233). It shows the complete terpene character.

Most of these terpenes undergo oxidation on exposure to moist air, i.e. they undergo autoxidation (Chap. XLVIII, J.). Thus limonene yields carvone, carveol, and other products (B., 1914, 2623).

## 2. ALCOHOLS AND KETONES

**Menthol**, *p*-menthan-3-ol, mint camphor,  $\text{C}_{10}\text{H}_{20}\text{O}$ , has the structure I given by *Brühl* in 1888.

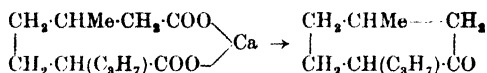


The *l*-modification is the chief constituent of oil of peppermint. It melts at  $43^\circ$ , has a strong odour of peppermint, and is used as an antiseptic and anæsthetic. When heated with copper sulphate it yields cymene, when reduced with hydriodic acid, hexahydrocymene, and on oxidation with permanganate it yields  $\beta$ -methyladipic acid, and several fatty acids. As the formula contains three asymmetric carbon atoms, eight optically active, i.e. 4 pairs of stereoisomerides are possible, and 3 such pairs have been isolated.

A *d*-*l*-menthol is obtained by the catalytic hydrogenation of thymol (p. 483) (cf. J. C. S., 1912, 109).

The corresponding ketone **menthone**, *menthan-3-one*,

$C_{10}H_{18}O$ , is obtained when the alcohol is oxidized with dichromate (*Beckmann*, A., 1891, **262**, 31), and also occurs in oil of peppermint. It boils at  $207^{\circ}$ , and has the characteristic properties of a ketone; its **semicarbazone** melts at  $184^{\circ}$ . It is readily converted into thymol (1-methyl-3-hydroxy-4-isopropyl-benzene) by bromination and elimination of hydrogen bromide, and when oxidized yields  $\beta$ -methyladipic acid. Hence follows the constitution, which is supported by its synthesis by the distillation of calcium  $\beta$ -methyl- $\alpha'$ -isopropylpimelate (*Kötz* and *Schwarz*, A., **357**, 206):



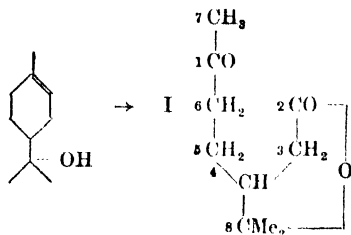
Two inactive (racemic) isomerides are possible, viz. *cis* and *trans* forms, i.e. the H atoms attached to C atoms 1 and 4 lie in the same plane in the *cis* and in different planes in the *trans*, and in all probability ordinary *d-l*-menthone is the *trans* form. By solution in concentrated sulphuric acid and precipitation with ice it yields the *iso*- or *cis*-menthone (cf. J. C. S., 1910, 1760).

**Carvomenthol**, *p*-menthan-2-ol, isomeric with menthol, does not occur naturally but is obtained by reducing carvone. For stereo-isomeric forms cf. *Gaz.*, 1925, 818.

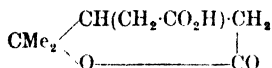
**Terpineol**.—The name was originally given to the mixture of alcohols formed by the dehydration of the glycol terpin, 1-8-dihydroxy-menthane. Four such compounds are theoretically possible and three are known, viz.  $\alpha$ -,  $\beta$ -, and  $\gamma$ -terpineols.

$\alpha$ -**Terpineol**,  $\Delta^1$ -menthen-8-ol, occurs both in free form and as esters, and is obtained readily from natural products, e.g. by the action of dilute potash on limonene hydrochloride, or by the hydration of pinene hydrate. It has m.-pt.  $37^{\circ}$ , b.-pt.  $218^{\circ}$ , and  $[\alpha]_D - 106^{\circ}$ . It forms a *phenylurethane*, m.-pt.  $113^{\circ}$ , a *nitrolpiperide*, m.-pt.  $159^{\circ}$ – $160^{\circ}$ . By catalytic reduction it can yield *p*-menthan-8-ol, *p*-menthane or dipentene, according to conditions. When treated with dilute acids it can give dipentene, terpinolene, terpinene, terpin hydrate, cineol or cymene, according to the conditions. Its constitution is of importance, as those of several terpenes are deduced from that of terpineol. The constitution is based on

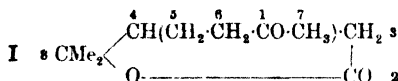
(1) examination of its decomposition products, (2) its synthesis.



By means of dilute permanganate two hydroxyls are added to the double bond, and 1 : 2 : 8-trihydroxy-menthane (trihydroxy-hexahydro-*p*-cymene) is formed, and this on further oxidation yields a ketolactone, homoterpenyl methyl ketone (I) (by the fission at C atoms 1 and 2), which can be oxidized to acetic and terpenylic acids. The constitution of the latter has been proved to be:

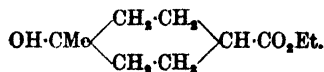


from its method of synthesis (*Simonsen*, J. C. S., 1907, 184).



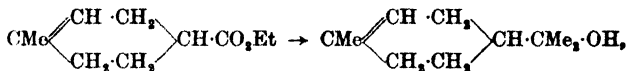
Homoterpenyl methyl ketone must have the formula I, and hence the 1 : 2 : 8-positions of the three hydroxyl groups in the first oxidation product, and the  $\Delta^1$ -position of the ethylene linking and position 8 of the hydroxyl group in terpineol.

Its synthesis (*Perkin*, J. C. S., 1904, 654) is from  $\delta$ -keto-hexahydrobenzoic acid (4-keto-cyclohexane-carboxylic acid). The ester of this acid reacts with magnesium methyl iodide, and then with water, yielding:



By the action of fuming hydrobromic acid the hydroxyl is replaced by bromine, and then, by the action of pyridine, hydrogen bromide is eliminated and  $\Delta^3$ -tetrahydro-*p*-toluic acid

is formed. The ethyl ester of this acid reacts with magnesium methyl iodide, and then with water, in the normal manner, yielding the tertiary alcohol, inactive terpineol:



and by the elimination of water dipentene is obtained.

This method of synthesis has been extended by *Perkin* and his students to a large number of cases, and they have obtained alcohols and unsaturated hydrocarbons analogous to the natural products, which, so far, have not been obtained naturally. From  $\Delta^1$ -tetrahydro-*p*-toluic acid,  $\Delta^3$ -*p*-menthen, and  $\Delta^{1:8(9)}$  menthadiene. From hexahydro-*o*-toluic acid, compounds similar to terpineol and dipentene were obtained, but with the substituents in *o*-positions. From hexahydrobenzoic acid a compound was obtained analogous to dipentene, but without the methyl substituent in position 1. By using optically active  $\Delta^1$ -tetrahydro-*p*-toluic acid, an active alcohol and terpene were synthesized. (J. C. S., 1905, 639, 655, 661, 1067, 1083; 1906, 832, 839; 1908, 573, 1871, 1876; 1910, 2129, 2147; 1911, 118, 518, 526, 727, 741. For another method of synthesis of hydrocarbons allied to terpenes cf. *Haworth* and *Fyfe*, J. C. S., 1914, 1659.)

**Terpin**, *p*-mentha-1:8-diol, has been synthesized by the action of magnesium methyl iodide on both carbonyl groups of ethyl cyclohexanone-4-carboxylate (*Kay* and *Perkin*, J. C. S., 1907, 372), and is also formed by boiling terpineol with dilute sulphuric acid. It exists in two stereo-isomeric modifications, *cis* and *trans*. The *cis* is the common form, and combines with water to give **terpin hydrate**,  $\text{C}_{10}\text{H}_{22}\text{O}_3$ , which forms well-developed crystals, m.-pt. 116°. When dehydrated the terpins yield terpinene, terpinolene, terpineol, and cineol (p. 972).

**d-Piperitone**,  $\Delta^1$ -menthen-3-one, occurs (80 per cent) in the oil of the grass *Andropogon Iwarancusa* and the corresponding *dl*-compound in oils from certain species of eucalyptus (J. C. S., 1921, 779, 1644; 1922, 1872; 1923, 2268). It is characterized by the readiness with which it racemizes and the structure has been proved by an examination of its oxidation products, viz.  $\alpha$ -isopropylglutaric acid and  $\alpha$ -hydroxy- $\alpha$ -methyl- $\alpha'$ -isopropyladipic acid,  $\text{CHMe}_2 \cdot \text{CH}(\text{CO}_2\text{H}) \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CMe}(\text{OH}) \cdot \text{CO}_2\text{H}$ .

**Pulegone**,  $\Delta^{4(8)}$ -*p*-menthen-3-one, occurs in oil of pennyroyal from *Mentha Pulegium* and *Hedeonia pulegioides*. It is isomeric with camphor and its hydrobromide melts at  $40\cdot3^\circ$ . When reduced it yields menthone. Its oxidation products are acetone and  $\beta$ -methyladipic acids, and when heated with water it yields acetone and 1-methylcyclohexan-3-one.

**Carvone**,  $\Delta^{6:8(9)}$ -menthadien-2-one, is the chief constituent of oil of caraway seeds and dill oil, and is widely distributed in the vegetable kingdom. It is a liquid, distils at  $228^\circ$ , exists in *d*- and *l*-modifications, and has the properties of an unsaturated ketone (cf. A., 1897, 297, 122). With hydroxylamine it yields carvoxime, which is identical with nitroso-limonene. When heated with phosphoric acid carvone yields carvacrol.

**Diospenol** (*Buchu camphor*),  $C_{10}H_{16}O_2$ ,  $\Delta^1$ -*p*-menthen-2-ol-3-one, from the buchu leaves of species of *Barosina*, is an unsaturated hydroxy-ketone; it has m.-pt.  $83^\circ$ , b.-pt.  $109^\circ/10$  mm., and its molecular refraction shows appreciable exaltation. On oxidation it yields  $\alpha$ -isopropyl- $\gamma$ -acetylbutyric acid,  $CO_2H\cdot CH(CHMe_2)\cdot CH_2\cdot CH_2\cdot CO\cdot CH_3$  (B., 1906, 1160). It can react as the tautomeric 2:3-diketone as it forms a *dioxime*, m.-pt.  $197^\circ$ .

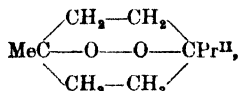
### 3. ALDEHYDES

A few aldehydes belonging to this group occur in nature, e.g. **Phellandral**, 4-isopropyl- $\Delta^1$ -cyclohexen-1-aldehyde, in water dropwort and in certain species of eucalyptus, and the  $\Delta^2$ -isomeride **Cryptal**, which also occurs in species of eucalyptus.

### 4. CINEOLES

Characteristic oxides of dihydric alcohols are known under the name of cineoles. The one which occurs naturally is the 1:8-cineole, i.e. the anhydride of *p*-menthane-1:8-diol. It is present in wormseed oil, from *Artemisia maritima*, and in certain eucalyptus oils. It has m.-pt.  $1^\circ$ , b.-pt.  $174\cdot4^\circ$ , and is relatively stable. It is dehydrogenated to *p*-cymene. The *hydrobromide* melts at  $56^\circ$ – $57^\circ$ . It forms additive compounds with phenols, e.g. with *o*-cresol,  $C_{10}H_{18}O$ ,  $C_7H_8O$ , m.-pt.  $55\cdot5^\circ$ , and with resorcinol  $(C_{10}H_{18}O)_2$ ,  $C_6H_8O_2$ , m.-pt.  $80^\circ$ – $85^\circ$ . It forms characteristic hydrochloride, phosphate and arsenate which are used in its estimation. It usually accompanies  $\alpha$ -pinene and  $\alpha$ -terpineol in natural oils, and can be prepared

by the elimination of water from terpin, and hence its structure. 1:4-**Cineole**, the *anhydride* of *p*-menthane-1:4-diol, boils at 172°. With HBr it is gradually converted into terpinene dihydrobromide, m.-pt. 58°-59°. It can be obtained from ascaridole by addition of hydrogen and subsequent dehydration. **Ascaridole**,  $\Delta^2$ -*p*-menthene 1:4-dioxide,



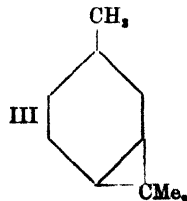
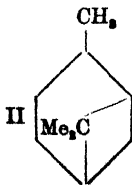
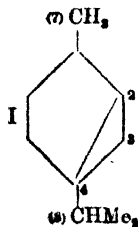
obtained from chenopodium oil, has b.-pt. 96°-97°/8 mm., and its structure follows from the readiness with which it is hydrogenated to 1:4-terpin.

### C. Dicyclic or Bridged Terpenes and Oxygenated Compounds

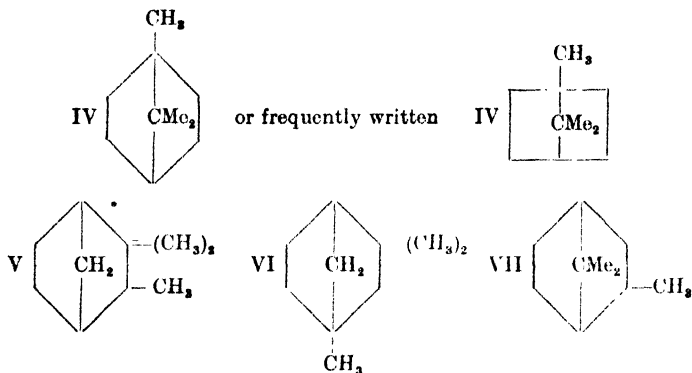
These compounds are more complex than the monocyclic terpenes. They consist of two condensed rings with two or three carbon atoms in common, and the rings may be 3-, 4-, 5- or 6-membered rings. They may also be regarded as derived (a) from *p*-menthane by the direct union of two carbon atoms and the formation of a simple bridge, or (b) from methylated cyclohexanes by bridging with a  $\text{CH}_2$  or  $\text{CMe}_2$  bridge.

The chief groups are:

I	Thujane	<i>p</i> -menthane with direct union between 2 and 4.
II	Pinane	" " " 2 and 8.
III	Carane	" " " 3 and 8.
IV	Camphane	" " " 1 and 8.
V	Isocamphane and	Trimethylcyclohexane with a $\text{CH}_2$ bridge.
VI	Fenchane	
VII	Isobornylane	Methylcyclohexane with a $\text{CMe}_2$ bridge.







The terpenes found naturally are in practically all cases unsaturated and contain one or two olefine links, and some are characterized by the readiness with which they undergo complex changes into isomerides; cf. the *Wagner-Meerwein* transformation (p. 978). The commonest of the hydrocarbons is  $\alpha$ -pinene derived from II, and the most important oxygen compound camphor derived from IV.  $\alpha$ - and  $\beta$ -Pinenes are the parent hydrocarbons of all terpenes as by ring fission they can give dipentene (p. 963), and by molecular rearrangement into borneol derivatives (i.e. camphane compounds) and camphene (a derivative of isocamphane) can be obtained from borneol.

### 1. TERPENES

**$\alpha$ -Pinene**,  $C_{10}H_{16}$  (I. p. 975), is the chief constituent of German and American oil of turpentine, oil of juniper, eucalyptus, oil of sage, &c. It forms, together with  $\beta$ -pinene, sylvestrene, and dipentene, Russian and Swedish turpentine oil.

Oil of turpentine is obtained by distilling turpentine, the resin of pines, with steam, colophonium (fiddle resin) (Chap. XXXII, B3) remaining behind. It is a colourless, strongly refracting liquid of characteristic odour, almost insoluble in water but readily soluble in alcohol and ether. It dissolves resins and caoutchouc (being therefore used for the preparation of oil paints, lakes), also sulphur, phosphorus, &c. Pinene absorbs oxygen from the air with the formation of  $H_2O_2$  and production of resin, minute quantities of formic acid, cymene, &c., being formed at the same time. Dilute nitric acid gives rise either

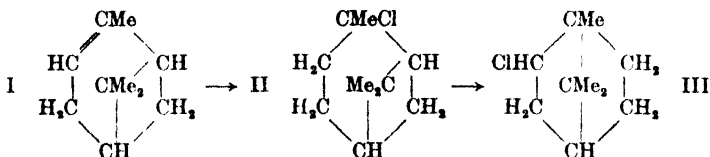
to terephthalic acid in addition to fatty acids, or—under other conditions—to terpenylic acid (p. 970),  $C_8H_{12}O_4$  (which belongs to the fatty series). Heating with iodine transforms it into cymene, the action being violent. It acts as an antiseptic, and arrests the secretions (e.g. that of the kidneys).

It exists in *d*, *l* and *dl* forms: *d*-pinene or australene occurs in large quantities in German, Russian, and Swedish oils; *l*-pinene or terebenthene in French turpentine oil; *d-l*-pinene is obtained by heating pinene nitroso-chloride with aniline.

*d*- or *l*- $\alpha$ -Pinene has b.p.  $156^\circ$ ,  $n_D^{20} \pm 45^\circ$ , and  $d_4^{20}$  0.858, the *d-l* form has the same boiling-point and density.

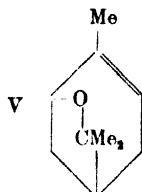
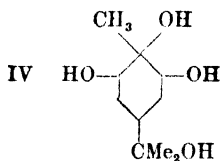
The presence of a double bond in the pinene molecule is indicated by the formation of **dibromides**, an oil and a solid melting at  $169^\circ$ , and also by the formation of a glycol, **pinene glycol**,  $C_{10}H_{16}(OH)_2$ , by the action of dilute permanganate, and of a **nitroso-chloride** ( $C_{10}H_{16}, NOCl$ )<sub>2</sub>, colourless crystals melting at  $103^\circ$ , used for isolating pinene from mixtures. This yields a **nitropiperide**, m.p.  $118^\circ$ .

**Hydrochloride**,  $C_{10}H_{17}Cl$ . At temperatures below  $0^\circ$  pinene I forms the normal hydrochloride II by the addition of H and Cl to the olefine bond, H to CH and Cl to CMe, but at  $0^\circ$  or higher temperatures the actual product is isobornylchloride III, formed by molecular rearrangement (termed the *Wagner-Meerwein* rearrangement).



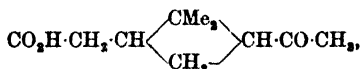
The constitution of pinene is based largely upon that of **pinole**,  $C_{10}H_{16}O$ , a product obtained by the elimination of water by the aid of dilute mineral acids, from **sobrerol**,  $C_{10}H_{16}(OH)_2$ , which is formed when pinene is left exposed to sunlight in contact with air and water. With dilute permanganate, pinole, which is an unsaturated ether, yields **pinole-glycol**,  $C_{10}H_{16}O(OH)_2$ , and this on further oxidation yields a tetrahydric alcohol IV, **sobrerithritol**, *p*-**menthane-1:2:6:8-tetrol**,  $C_{10}H_{16}(OH)_4$ , which can be oxidized to terpenylic and terebic acids. Oxidation with chromic acid yields **hydroxycarvone**. Sobrerol is thus the unsaturated glycol

$\Delta^1$ -*p*-menthen-6:8-diol, and pinole the anhydride of this, viz. V (Wagner).

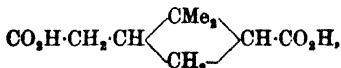


When boiled with dilute acids pinene yields terpineol or its esters; such a transformation is explicable if the assumption is made that the four-membered ring is unstable, and that a rupture between the  $\text{CMe}_2$  and upper  $\text{CH}$  group occurs. A similar rupture, accompanied by the wandering of a chlorine atom, occurs in the transformation of pinene nitroso-chloride into hydrochlorocarvoxime under the influence of hydrochloric acid.

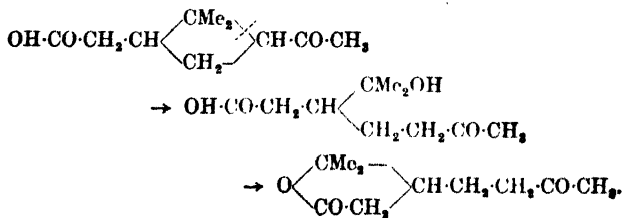
When pinene is oxidized with permanganate the double linking is broken and a monobasic ketonic acid,  $\alpha$ -pinonic acid,



is formed, and this on further oxidation with hypobromite yields the dibasic acid, *cis*-pinic acid,



from which *cis*-norpinic acid, 1:1-dimethyl-cyclobutane-2:4-dicarboxylic acid, can be obtained (Baeyer, B., 1896, 1907), indicating that the four-membered ring is stable in the presence of oxidizing agents, although readily ruptured by hydrolysing agents, e.g. pinonic acid yields when hydrolysed a lactone, homoterpenyl methyl ketone (cf. p. 970).

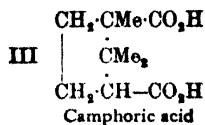
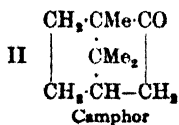
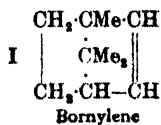


The structure of the norpinic acid has been further proved by the synthesis of the *trans* isomeride by *Kerr* (J. A. C. S., 1929, 614) and the conversion into the *cis*-anhydride and then into the *cis*-acid.

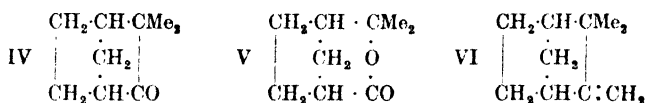
The only reactions of pinene difficult to account for by means of *Wagner's* formula are its oxidation to isoketocamphoric acid, isocamphoronic acid, and terebic acid (*Tiemann* and *Semmler*, B., 1896, 529, 3027; *Perkin*, Proc., 1900, 214).

The isomeric  $\beta$ -pinene (*l*-nopinene) with the double bond in position 1:7, occurs in many turpentine, e.g. French oil, 37 per cent. It has  $[\alpha]_D - 22.4^\circ$ , but yields no crystalline derivatives. On oxidation it yields products quite different from those obtained from  $\alpha$ -pinene. The first product, with permanganate is the glycol, which then gives an  $\alpha$ -hydroxy acid  $\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{OH} \rightarrow \cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$  (**nopinic acid**), and finally a ketone  $\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H} \rightarrow \cdot\text{CO}$  and  $\text{CO}_2$ . The ketone **nopinone**, CO in place of  $\cdot\text{CH}:\text{CH}_2$  in  $\beta$ -pinene, yields a *semi-carbazone*, m.-pt.  $188^\circ$ , and on oxidation with nitric acid both rings are ruptured and the lactone acid, homoterpenylic acid (p. 970), is formed.  $\beta$ -Pinene can be synthesized from this ketone, and nopinic acid with dilute mineral acids gives dihydrocuminic acid which oxidized with ferricyanide yields cumic acid (*p*-isopropylbenzoic acid).

**Bornylene**,  $\text{C}_{10}\text{H}_{16}$ , is obtained by the action of alcoholic solutions of potassium hydroxide, but particularly of potassium amyloxyde at  $190^\circ$  on bornyl iodide (from pinene and HI). As it is readily oxidized to camphoric acid III it is represented by formula I. By the dehydration of borneol and isoborneol, the alcohols corresponding with bornyl and isobornyl iodides, camphene (p. 978) is formed, but when the methyl ester of bornyl or isobornyl methyl xanthate ( $\cdot\text{CH}\cdot\text{O}\cdot\text{CS}_2\cdot\text{CH}_3$ ) is distilled, the main product is bornylene with some of the isomeride tricyclene (this Chap., D.). It has m.-pt.  $113^\circ$ , b.-pt.  $146^\circ$ , and  $[\alpha]_D - 21.7^\circ$  (in toluene) and yields a *nitrosite*, m.-pt.  $163^\circ$ . On catalytic hydrogenation it yields camphane, and with hydrogen chloride it yields  $\delta$ -chlorocamphane, m.-pt.  $138^\circ$ .

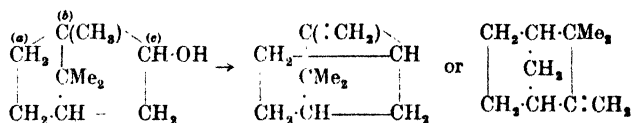


**Camphene**, *d* and *l*, is a solid, m.-pt.  $51^{\circ}$ – $52^{\circ}$  and  $[\alpha]_D - 85^{\circ}$ . It can be obtained from pinene by combining with hydrogen chloride, forming bornyl chloride, and then removing hydrogen chloride by means of alkalis. Using the iodide the product is a mixture of bornylene and camphene. For some years it was represented by formula I, but it does not yield camphoric acid when oxidized. *Harries* and *Palmen* (B., 1910, 1432) have shown that it forms an ozonide when its acetic-acid solution is saturated with ozone, and that this when warmed yields a mixture of camphenilone (30 per cent) (IV), and the lactone dimethylnorcampholide (50 per cent) (V), and they



therefore favour *Wagner's* formula VI for camphene. The formation of the lactone V is due to a secondary reaction, viz. the formation of the peroxide of IV, and then by fission and subsequent ring formation.

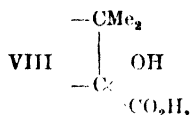
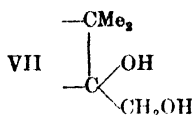
The formation of camphene from bornyl chloride must involve rearrangements within the molecule. *Meerwein* (A., 1914, 405, 129) represents the change, generally termed the *Wagner-Meerwein* rearrangement, as follows:



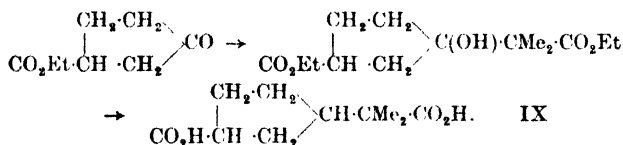
The change thus consists in a union between C atom *a* and *c* with the formation of a tricyclic system by the loss of  $\text{H}_2\text{O}$ , followed by a scission between *a* and *b*, by the addition of H to *a*, and OH to *b*, and finally the elimination of water the OH from *b* and the H from the  $\text{CH}_3$  attached to *b*. This has been shown to be improbable as tricyclene postulated as the intermediate is a stable compound more stable than camphene, and *Robinson* suggests electronic changes comparable with the pinacol-pinacone change (Chap. XXXVIII).

The molecular refraction (*Auwers*, A., 1912, 387, 240) agrees with *Wagner's* formula. Its oxidation products are

(a) camphenilone (IV) (oxidation of  $C:CH_2$  to  $CO$ ); (b) 1 per cent permanganate on a benzene solution, the glycol (VII),



which can be readily oxidized to camphenylic acid (VIII); (c) with nitric acid, camphoric acid (III), and finally 2:2-dimethyl-cyclopentane-1:1:3-tricarboxylic acid. **Camphenic** acid, 3-carboxy-cyclopentyle-1-iso-butyric acid IX, has been synthesized by *Lipp* (B., 1914, 871) from ethyl cyclopentane-1-one-3-carboxylate and ethyl  $\alpha$ -bromoiso-butyrate in the presence of zinc; then eliminating water from the hydroxy ester, and reducing the resulting unsaturated ester with hydrogen and platinum black.

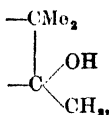


The reactions of camphene and bornylene with ethyl diazoacetate confirm the formulæ I and VI. The normal reaction with unsaturated compound is for nitrogen to be eliminated and the formation of a cyclopropane ring between the C atom of the  $CH_2$  group of the diazo-ester, and the two C atoms united by the olefine linking. Camphene, if represented by formula VI, should thus give a compound containing the

grouping,  $\begin{array}{c} \diagup C-CH_2 \\ \diagdown \quad / \\ \quad CH \cdot CO_2H \end{array}$ , and this on final oxidation should

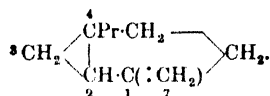
yield cyclopropane-1:1:2-tricarboxylic acid, whereas if it has the structure represented by formula I, originally attributed to camphene but now assigned to bornylene, it should yield as final oxidation product cyclopropane-1:2:3-tricarboxylic acid. In reality it has been found that camphene gives the 1:1:2-tricarboxylic acid and bornylene the isomeric 1:2:3-acid (*Büchner and Weigand*, B., 1913, 759, 2108).

Camphenilone (IV, p. 978) has been synthesized, and this with  $\text{MgBrCH}_3$  gives tertiary alcohol



which undergoes dehydration with dilute sulphuric acid yielding camphene.

**Sabinene**,  $\Delta^{10}$ -*thujene* (cf. I, p. 973), occurs in marjoram oil; it has b.-pt.  $163^\circ\text{--}165^\circ$  and  $[\alpha]_D + 80^\circ$ . It forms a hydrochloride and a nitroso-chloride. Its oxidation products closely resemble those of camphene. It can yield a ketone by the replacement of the  $>\text{C}:\text{CH}_2$  by  $>\text{CO}$ , glycol  $>\text{C}(\text{OH})\cdot\text{CH}_2\cdot\text{OH}$ , and a hydroxy acid, sabinenic acid,  $>\text{C}(\text{OH})\cdot\text{CO}_2\text{H}$ . Its close relationship to the thujenes is shown by its catalytic reduction to thujane and hence contains a 3 carbon ring:



The tri-ring is readily ruptured, as sabinene and its derivatives can be transformed into terpinene and related hydroxy compounds.  $\alpha$ - and  $\beta$ -**Thujenes**,  $\text{C}_{10}\text{H}_{16}$  (*Tschugaeff*, B., 1901, 2279; 1904, 1481), also contain a tri-ring and respectively  $\Delta^1$  and  $\Delta^2$  thujene.

## 2. ALCOHOLS AND KETONES

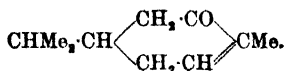
The most important member of this group is:

**Common or Japan camphor**,  $\text{C}_{10}\text{H}_{16}\text{O}$ , which is found in the camphor tree (*Laurus camphora*), and can be obtained by steam distillation of the wood. It forms colourless, transparent, glistening prisms of characteristic odour. It melts at  $179^\circ$ , boils at  $204^\circ$ , has a sp. gr. 0.985, and can be sublimed readily. It is dextro-rotatory in alcoholic solution, the amount of rotation varying with the concentration. When distilled with phosphoric anhydride it yields cymene; zinc chloride at high temperatures also transforms camphor into cymene, though in the latter case the reaction is less simple:

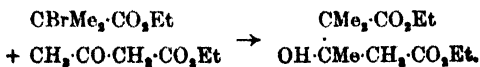


When heated with iodine it yields **carvacrol**, i.e. hydroxycymene (p. 483), just as oil of turpentine yields cymene. Nitric acid oxidizes it to the dibasic **camphoric acid**,  $C_8H_{14}(CO_2H)_2$  (III, p. 977), which somewhat resembles phthalic acid (see B., 1890, 218), and then to **camphoronic acid**, unsym. trimethyl-carballylic acid, &c. Camphor yields **camphor-oxime**,  $C_{10}H_{16}(NOH)$ , m.-pt.  $119.5^\circ$ , and a **semicarbazone**, m.-pt.  $245^\circ$ , and therefore contains a carbonyl group, and with nitrous acid it forms **isonitroso-camphor**,  $C_{10}H_{14}O:N\cdot OH$ , and thus contains the group  $\cdot CH_2\cdot CO$ . The oxime by the loss of water is converted into the **cyanide**,  $C_9H_{15}\cdot CN$ , which yields **campholenic acid**,  $C_9H_{15}\cdot CO_2H$ , on saponification, and **camphylamine**,  $C_9H_{15}(CH_2\cdot NH_2)$ , on reduction (B., 1888, 1125).

A considerable amount of attention has been devoted by various chemists to the question of the constitution of camphor (*Lapworth*, B. A. Report, 1900, 299). At first, great importance was attached to the readiness with which camphor can be transformed into benzene derivatives, e.g. cymene and carvacrol, and attempts were made to represent it as a simple six-carbon ring compound, e.g. *Kekulé*,

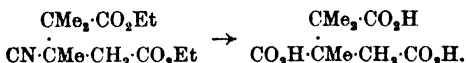


whereas others represented it as a bridged six-carbon ring. In 1893 *Bredt* suggested the formula II (p. 977), which is now generally accepted, and which has been confirmed recently by the synthesis of camphoric acid. *Bredt* drew especial attention to the oxidation products of camphor, namely camphoric, camphoronic, and trimethyl-succinic acid previously obtained by *Koenigs*. He showed that camphoronic acid when heated gave trimethyl-succinic, isobutyric, and carbonic acids and carbon, and suggested the formula  $CO_2H\cdot CH_2\cdot CMe(CO_2H)\cdot CMe_2\cdot CO_2H$ , viz.  $\alpha$ - $\alpha$ - $\beta$ -trimethyl-carballylic acid, a constitution which has since been confirmed by *W. H. Perkin* and *Thorpe's* synthesis (J. C. S., 1897, 1169). This consists in condensing ethyl acetoacetate and ethyl  $\alpha$ -bromo-isobutyrate by means of zinc to ethyl  $\beta$ -hydroxy- $\alpha$ - $\alpha$ - $\beta$ -trimethyl glutarate:

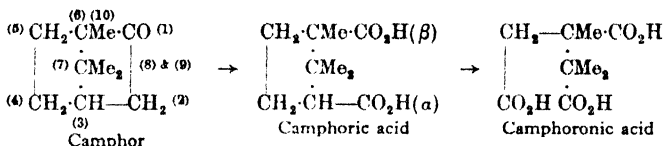




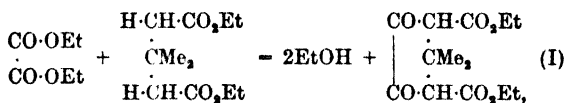
The OH group is replaced by Cl, and this by CN, and the cyano-ester when hydrolysed yields camphoronic acid:



The relationship between camphor and its oxidation products is thus simple, as shown by the following scheme:



Camphoric acid has been synthesized by *Komppa* (B., 1901, 2472; 1903, 4332; J. C. S., 1911, 2010). Ethyl oxalate and ethyl  $\beta\beta$ -dimethyl-glutarate condense in the presence of sodium ethoxide, yielding diketo-apocamphorate I:



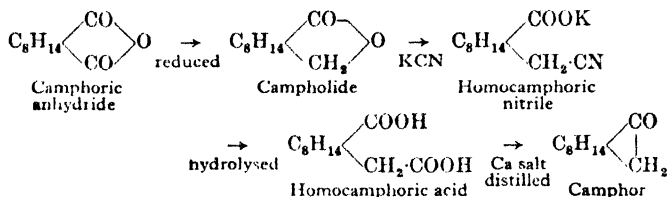
which, methylated by means of sodium and methyl iodide, yields the ethyl ester of diketo-camphoric acid II:



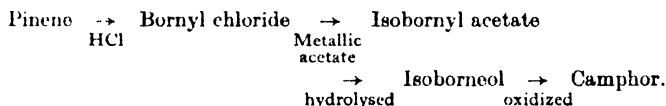
and this can be reduced with sodium amalgam to dihydroxy-camphoric acid; further reduction with phosphorus and hydriodic gives dehydro-camphoric acid, III, which combines with hydrogen bromide; and the  $\beta$ -bromo-camphoric acid thus obtained, when reduced with zinc and acetic acid, yields the racemic modification of camphoric acid.

A synthesis from  $\text{CMe}_2 \begin{array}{l} \text{CH}(\text{CO}_2\text{H}) \cdot \text{CH}_2 \\ \text{CH}(\text{CO}_2\text{H}) \cdot \text{CO} \end{array}$ , has been accomplished by somewhat similar steps (*Perkin and Thorpe*, J. C. S., 1904, 146; 1906, 799).

Camphor can be synthesized from camphoric acid by the following series of reactions (*Haller*, C. R., 1896, 122, 446):



Considerable amounts of camphor (mainly *dl* form) are manufactured from pinene by the following series of reactions (*J. I. E. C.*, 1934, 589):

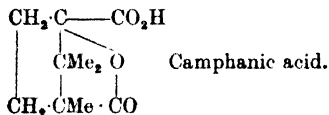


To obtain good yields it is essential to use pure pinene and carefully to control the reactions, especially the final oxidation with nitric and sulphuric acids. Several factories produce camphor by this process, but their output varies enormously with the price of the natural products. Camphor is used in medicine and for the manufacture of celluloid.

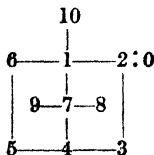
Camphoric acid is an unsymmetrical dibasic acid, as it gives two isomeric monomethyl esters and two amic acids. One carboxylic acid is probably attached to a tertiary and the other to a secondary carbon atom, as the acid yields a single *monobromo* substituted derivative when subjected to the *Hell-Volhard-Zelinsky* method of bromination. The derivatives are known respectively as  $\alpha$  and  $\beta$  (or *ortho* and *allo*), the  $\alpha$ -methyl ester, for example, contains the group  $>\text{CH}\cdot\text{CO}_2\text{Me}$ , and the  $\beta$ -methyl ester the group  $>\text{C}\cdot\text{CO}_2\text{Me}$ . As isonitroso-camphor— $\text{C}(\text{:NOH})\cdot\text{CO}$ —when warmed with hydrochloric acid yields  $\alpha$ -camphoramidic acid,  $>\text{CH}\cdot\text{CO}\cdot\text{NH}_2$ ; it follows that the methylene group of camphor corresponds with the  $\alpha$ -carboxylic group in camphoric acid.

As the camphoric acid molecule contains two centres of dissymmetry it exists in four optically active and two racemic modifications, the latter known respectively as *dl*-camphoric and *dl*-isocamphoric acids. The properties of the acids are:

*d*- and *l*-camphoric, m.-pt. 187°, and  $[\alpha]_D \pm 47.8^\circ$ ; *dl*-camphoric, m.-pt. 202°–203°; *d*- and *l*-isocamphoric, m.-pt. 171°–172°, and  $[\alpha]_D \mp 47.1^\circ$ ; *d*-*l*-iso acid, m.-pt. 191°. To obtain complete racemization of *d*-camphoric acid it is necessary for epimerization to occur at both centres; when epimerization at one centre occurs then a certain amount of the *d*-isocamphoric acid is formed. Camphor, on the other hand, exists in two active and one racemic form only, and on catalytic reduction yields an optically inactive camphane. The dissymmetry is due to the presence of the CO group. In the oxidation of camphoric acid to camphoronic acid, **camphanic acid**, the lactone of  $\alpha$ -hydroxy-camphoric acid is formed as an intermediate product; its constitution follows from the fact that it is formed by boiling bromo-camphoric anhydride with water.



Numerous mono- and disubstituted derivatives of camphor are known. The isomeric mono-substituted compounds are often termed  $\alpha$ ,  $\beta$ , and  $\pi$ , but it is preferable to denote the number of the carbon atom to which the substituent is attached according to the scheme where the C of the CO group is 2. Then the prefixes  $\alpha$ ,  $\beta$  and  $\pi$  correspond respectively with the 3-, 10-, and 8-positions.



The first product of chlorination, bromination or nitration is always a 3-substituted compound, and frequently a mixture of two stereo-isomeric products as the two hydrogens attached to C No. 3 are not absolutely equivalent. The further product is usually a 3:3-disubstituted derivative, and when the two substituents are different a mixture of two stereo-isomeric products is often obtained, e.g. 3-bromo-3-nitro-camphor.

The two 3-bromo-camphors have much the same melting-points, viz.  $76^{\circ}$  and  $78^{\circ}$ , but very different rotations; in alcohol the 3-compound has  $[\alpha]_D + 165^{\circ}$  and the 3-*iso*-compound  $-40^{\circ}$ , and the addition of alkali to an alcoholic solution of either produces an equilibrium mixture of the two with  $[\alpha]_D + 147^{\circ}$ . A characteristic property of the camphorsulphonic acids is the readiness with which the sulphonyl chlorides and bromides lose  $\text{SO}_2$  when heated, yielding the corresponding chloro- and bromo-camphors, and this is often the most convenient method of preparing the 10- and 8-compounds.

The position of a substituent in the camphor molecule is often readily ascertained by an examination of the oxidation products, particularly the camphoric acids. Thus 3-substituted camphors yield camphoric acid itself, whereas 10- and 8-compounds yield the corresponding substituted camphoric acids. Among the camphor products of interest are:

(1) **Camphor-10-sulphonic acid** (*Reyehler's acid*), obtained by sulphonating camphor in acetic anhydride solution (cf. *Burgess and Lowry, J. C. S., 1925, 279*).

(2) *Kipping's* 3-bromo-camphor-8-sulphonic acid, obtained by sulphonating  $\alpha$ -bromo-camphor, is probably a mixture of the 3- and 3-*iso*-compounds.

Both the above acids are optically active strong monobasic acids, and are frequently used for resolving *dl*-bases into their active components (cf. Chap. L, A.).

(3) 3-**isonitro-camphor**, m.-pt.  $102^{\circ}$  and  $[\alpha]_D - 124^{\circ}$ , cannot readily be obtained by direct nitration as the chief products are oxidation products. It is best obtained by reduction of  $\alpha$ -bromo- $\alpha'$ -nitro-camphor with alcoholic potassium hydroxide. It shows marked mutarotation in the presence of traces of alkali (Chap. LXXI, I2), and this is due to the formation of the isonitro (or *pseudonitro*) group  $>\text{CH}\cdot\text{NO}_2 \rightarrow >\text{C}:\text{NO}\cdot\text{OH}$ . This acid form has not been isolated in a pure form, but numerous salts have. The bromo-compound  $>\text{CBr}\cdot\text{NO}_2$  does not exhibit mutarotation as it cannot yield the isonitro group (*Lowry* and others). A solution of 3-nitro-camphor when evaporated yields the anhydride of isonitro-camphor,  $>\text{C}:\text{NO}\cdot\text{O}\cdot\text{ON}:\text{C}<$ , m.-pt.  $193^{\circ}$ , and when this is heated above its melting-point camphorquinone is formed.

This diketone-camphorquinone (the CO groups in positions 2 and 3) is formed as above or by hydrolysing isonitroso-camphor with formaldehyde and hydrochloric acid and is an

intermediate in the oxidation of camphor to camphoric acid. It forms yellow needles, m.-pt.  $198^{\circ}$  and  $[\alpha]_D - 105^{\circ}$ , in chloroform, and is a typical  $\alpha$ -diketone and gives two pairs of stereo-isomeric oximes.

Camphor itself reacts as a typical ketone with the  $>\text{CH}_2\cdot\text{CO}<$  group. It forms an isonitroso-compound  $>\text{C}(\text{NOH})\cdot\text{CO}<$ ; it reacts in the enolic form  $>\text{CH}:\text{CH}(\text{OH})<$ , forms a sodium derivative which absorbs carbon dioxide, yielding camphor-carboxylic acid which is also obtained by hydrolysing  $\alpha$ -cyano-camphor, and hence has the carboxylic group in position 3. The 3-alkyl-camphors are formed by the action of alkyl iodides on sodio-camphor and 3-acyl-derivatives in a similar manner.

With *Grignard* reagents camphor forms tertiary alcohols. When reduced in neutral solvents with metallic sodium camphor yields a mixture of the stereo-isomeric secondary alcohols borneol and *iso*-borneol; the same products are found by catalytic hydrogenation, using nickel oxide at  $320^{\circ}$ – $350^{\circ}$  and high pressures. By using platinum black the product is mainly the *iso*-compound, viz. 80 per cent.

Isomeric with camphor is the compound termed  $\beta$ -camphor in which the C atom No. 2 has two hydrogens and C No. 3 an oxygen atom attached, i.e. the grouping  $>\text{CMe}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}<$  (cf. *Bredt* and *Perkin*, P., 1912, 56).

**Borneol and *iso*-Borneol.**—The borneols—the secondary alcohols corresponding with the ketone-camphor—exist in stereo-isomeric forms due to the spatial arrangements of the H and OH groups attached to C No. 2.\* They are known respectively as borneol and *iso*-borneol, and each exists in *d*, *l* and *dl* forms.

	m.-pt.	$[\alpha]_D$	m.-pt. of $\beta$ -nitro-benzoate
<i>d</i> - or <i>l</i> -Borneol ..	208.5°	$\pm 37.92^{\circ}$	137°
<i>dl</i> -Borneol ..	210.3	—	
<i>d</i> - or <i>l</i> - <i>iso</i> -Borneol	214	$\pm 34.1^{\circ}$ †	129

The three forms of borneol occur in various essential oils, whereas the *iso*-borneols do not. The *iso*-compounds are formed by the catalytic hydrogenation of camphor or by the hydration of camphene, e.g. the acetate by heating camphene

\* i.e. Whether the OH and the  $\text{CMe}_2$  bridge are on the same side of the cyclohexane ring or on opposite sides.

† Varies with solvent. The value given is for ethyl acetate solutions.

with sulphuric and acetic acids; in the latter case the product is almost completely racemized.

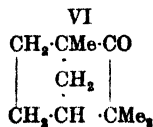
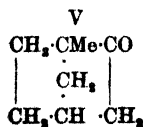
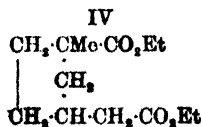
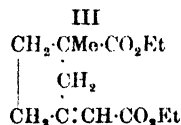
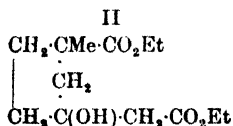
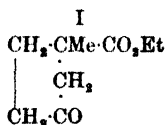
Both series of compounds are readily oxidized to camphor, and both on dehydration yield camphene, but *iso*-borneol more readily than borneol.

As alcohols they yield various esters, the *p*-nitro-benzoates are useful for identification and the chlorides are of technical importance. Bornyl chloride, m.-pt. 132°, is formed by the addition of HCl to pinene (*Wagner-Meerwein* change, p. 978) and is termed "artificial camphor". *Iso*-bornyl chloride, m.-pt. 161°, is formed by the addition of HCl to camphene.

The configurations of the two borneols or the two bornyl chlorides are not definitely established, but *Kommpa* and *Beckmann* (A., 1936, 522, 137) regard borneol as the *endo* and *iso*-borneol as the *exo* compound (cf. Chap. L, A7).

In the synthesis of camphor by oxidizing *iso*-borneol (cf. p. 983) a 97 per cent yield is obtained by using a nickel catalyst with 10 per cent of copper and iron oxides at 200°.

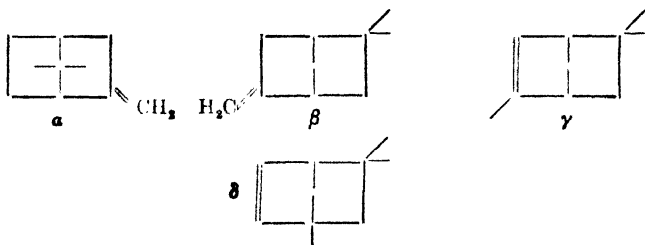
**Fenchone**,  $\alpha$ -methylcamphenilone, m.-pt. 5°–6° and  $[\alpha]_D + 64^\circ$ , is isomeric with camphor, occurs in fennel oil, is represented by *Semmler* (A., 1912, 387, 1) by formula VI (below), and its complete synthesis has been achieved (*Ruzicka*, B., 1917, 1362). Ethyl 1-methylcyclopentane-3-one-1-carboxylate (I), ethyl bromo-acetate and zinc yield ethyl 3-hydroxy-3-carbethoxymethyl-1-methylcyclopentan-1-carboxylate (II), which reacts with  $PBr_3$ , yielding the unsaturated ester, ethyl dehydromethylnorhomofenchonate (III), which is readily reduced to ethyl methylnorhomocamphorate (IV), and the lead salt of this heated in a current of  $CO_2$  yields methyl-norcamphor (V), which with excess of methyl iodide and soda-mide gives a mixture of fenchone (VI) and fenchosantanone (the monomethyl derivative):



Fenchone, unlike camphor, is resistant to *oxidizing* agents, and hence a study of degradation products is not easy. Digestion with sodamide, however, causes a fission in the ring at the  $>\text{CO}\cdot\text{CMe}_2<$ , yielding  $-\text{CO}\cdot\text{NH}_2$  and  $\cdot\text{CHMe}_2$  by the addition of ammonia. The product, the amide of fencholic acid, has been proved to be the amide of 1-methyl-4-*isopropylcyclopentane*-1-carboxylic acid. Due to the grouping

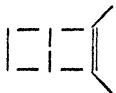
$\diagup\text{CMe}\cdot\text{CO}\cdot\text{CMe}_2\diagdown$  the carbonyl is not reactive, and the semicarbazone is formed extremely slowly. There is also no indication of enolization. It can be reduced catalytically to *l*-fenchyl alcohol and finally to fenchane.

**Fenchenes.**—By the dehydration of fenchyl alcohols or the elimination of hydrogen chloride from the chlorides a mixture of 4 isomeric fenchenes is obtained together with a tricyclic terpene. It is probable that none has been obtained pure, but from a study of degradation products they appear to have the structures:



In the formation of several of these a change in ring structure (*Walden-Meerwein* change) must occur, e.g. fenchyl alcohol  $\rightarrow$   $\alpha$ -fenchene.

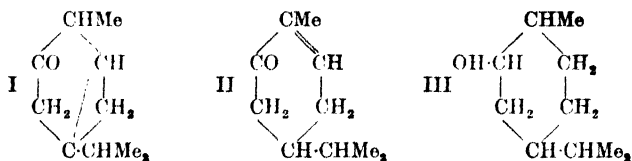
**Santene**,  $\text{C}_9\text{H}_{14}$ , is present in E. Indian sandalwood oil. Its *nitroso-chloride* melts at  $110^\circ$  and its *nitrosite* at  $123^\circ$ – $126^\circ$ . It contains one olefine link, and can be represented by the structure



as on oxidation it yields a glycol, then a diketone, and finally *cyclo-pentane*-1 : 3-dicarboxylic acid.

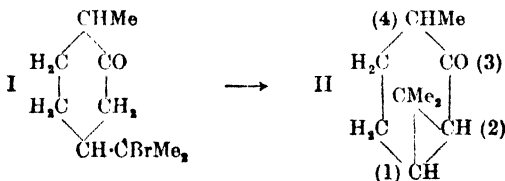
**Thujone** (I) occurs in thuja, wormwood, and sage oils; it is not unsaturated, and hence contains a dicyclic system; when

heated it forms carvotanacetone (II), and this is readily reduced to carvomenthol (III):

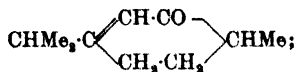


### The Carone Group

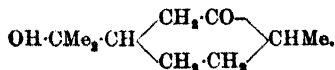
**Carone**,  $\text{C}_{10}\text{H}_{16}\text{O}$  (II), is one of the most important ring ketones of the terpene series, and is formed when dihydrocarvone hydrobromide, 8-bromomenthan-2-one (I), is treated with alcoholic potash (*Baeyer*, B., 1896, 5 and 2796).



It is a colourless oil with an odour of camphor and peppermint, and boils at  $210^\circ$ , but is, at the same time, partially transformed into the isomeric carvenone. The molecule, according to *Baeyer*, contains a six-carbon ring with a bridge. One of the most characteristic properties is the readiness with which the bridge is broken and derivatives of *p*- or *m*-menthane are produced. Thus when heated it yields carvenone or  $\Delta^3$ -*p*-menthen-2-one,

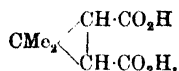


with hydrobromic acid it yields 8-bromo-menthan-2-one, and with sulphuric acid 8-hydroxy-menthan-2-one,

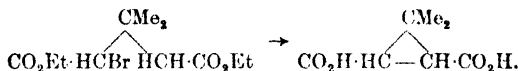




When oxidized with hot permanganate, carone yields a dibasic acid, **caronic acid** (*cis* and *trans* modifications, m.-pt. 174° and 212°), which *Baeyer* suggested was 1:1-dimethylcyclopropane-2:3-dicarboxylic acid,



a conclusion confirmed by *Perkin's* synthesis (J. C. S., 1899, 48) from ethyl dimethylacrylate,  $\text{CMe}_2\text{:CH}\cdot\text{CO}_2\text{Et}$ , and ethyl sodio-malonate (or ethyl sodio-cyanoacetate). The product, ethyl dimethylpropane-tricarboxylate,  $(\text{CO}_2\text{Et})_2\text{CH}\cdot\text{CMe}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ , when hydrolysed and heated at 200°, yields  $\beta\beta$ -dimethyl-glutaric acid,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CMe}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ . The  $\alpha$ -bromo-derivative of the ethyl ester of this acid,  $\text{CO}_2\text{Et}\cdot\text{CHBr}\cdot\text{CMe}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ , yields *cis* and *trans* caronic acids when heated with alcoholic potash:



The hydrocarbons  $\Delta^3$ - and  $\Delta^4$ -**carenes**,\*  $\text{C}_{10}\text{H}_{16}$ , have been isolated by *Simonsen*; the former from *Pinus longifolia* (J. C. S., 1920, 571), and the latter from the oil of *Andropogon Jwarancusa* (1922, 2294). The  $\Delta^3$  has b.-pt. 170° and  $[\alpha]_D + 7.7^\circ$ , and the  $\Delta^4$ , b.-pt. 165.5° and  $[\alpha]_D + 69^\circ$ . On oxidation both yield compounds containing the cyclopropane ring, the former giving caronic acid and the latter 1:1-dimethyl-2- $\gamma$ -ketobutylcyclopropane-3-carboxylic acid. On the other hand the cyclopropane ring is readily ruptured by acids and both hydrocarbons react with hydrochloric acid yielding mixtures of the hydrochlorides of dipentene and sylvestrene. The sylvestrene obtained from certain natural products apparently does not exist as such in the original material, but is formed from the carenes present by the method of treatment with hydrochloric acid. It is thus probable that derivatives of *m*-menthane do not occur in nature, but are products of intramolecular change (J. C. S., 1925, 2494).

With compounds containing a di- or tricyclic system, it must be remembered that in most cases the different rings do not lie in the same plane. This is most readily seen with the

\* See Carone formula, p. 689, for numbering.

aid of models, and holds good for camphor, camphene, fenchone. The usual single plane formulæ, therefore, do not represent the actual spatial relationships of the group.

In a survey of the dicyclic systems attention should be drawn to the stability of tri- and tetra-ring systems to oxidizing agents and their instability towards hydrolysing agents. By means of these reagents it is frequently possible to arrive at valuable information concerning the structure of a given dicyclic compound. By the aid of oxidizing agents simple derivatives of cyclopropane or cyclobutane can be formed, and by the aid of hydrolysing agents derivatives of cyclohexane.

### D. Tricyclic Terpenes

Attention has already been drawn to the possibility of the formation of a tricyclic system in the *Wagner-Meerwein* change (p. 978), and in the distillation of bornyl and *iso*-bornyl xanthates the bornylene is always mixed with some **tricyclene** I, and the same compound is present in the camphene obtained from borneol. It can be obtained by the action of zinc dust on pinene dibromide, 2:6-di-bromo-camphane. The simplest method is by the action of yellow mercuric oxide on camphor-hydrazone (B., 1920, 1815) in alkaline solution. It is very volatile, has m.-pt. 68°, b.-pt. 153°/761 mm., and by catalytic reduction yields *isocamphane*.

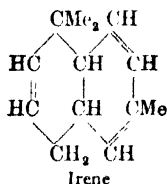
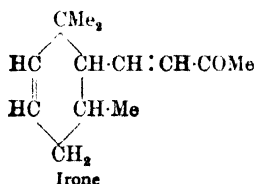
**Teresantalic acid**,  $C_{10}H_{14}O_2$ , present both free and as esters in E. Indian sandalwood oil, has a tricyclic structure. It melts at 157° and has  $[\alpha]_D - 76.6^\circ$  (in benzene). It is resistant to oxidizing agents, but with sulphuric acid readily yields santene,  $C_9H_{14}$  (p. 988). Its relationship to tricyclene is shown as follows: methyl teresantalate reduced gives an alcohol teresantalol; this with  $PCl_5$  gives teresantalyl chloride, which reduced with sodium and alcohol gives tricyclene, and hence teresantalic acid is represented by II.



## E. Irone and Ionones

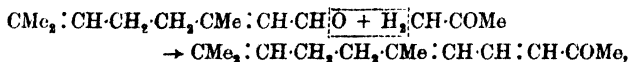
**Irone**—a methyl ketone,  $C_{13}H_{20}O$ —is the odoriferous principle of the iris root, and also probably of the violet. When boiled with hydriodic acid it yields the hydrocarbon **irene**,  $C_{13}H_{18}$ .

The formulæ suggested by *Tiemann* and *Krüger* are:

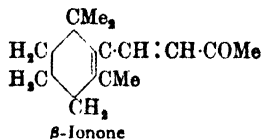
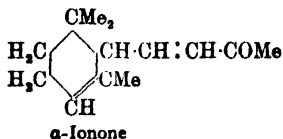


(cf. B., 1893, 2675). These chemists have synthesized two isomerides of irone, which they term  $\alpha$ - and  $\beta$ -ionones. These also possess the odour of violets, and are employed at the present time for the manufacture of violet and raspberry essence.

The synthesis consists in the condensation of citral (p. 958) with acetone to form the unsaturated ketone pseudo-ionone:



which is transformed into the ring compounds  $\alpha$ - and  $\beta$ -ionones when boiled with sulphuric acid and glycerol:

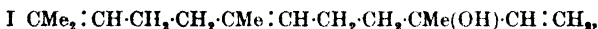


**Methyl-ionones** with  $\cdot\text{COEt}$  in place of  $\cdot\text{COMe}$  are formed when methyl ethyl ketone is used in place of acetone and have a still more pronounced raspberry odour.

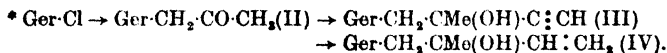
## F. Sesquiterpenes and related Oxygen Compounds

A detailed study of these compounds has been made within recent years, especially by *Ruzicka*, and the results published in *Helv.*, 1921–1936. Like the terpenes proper they may be divided into: (a) open-chain compounds with four olefine linkings; (b) monocyclic systems with three; (c) dicyclic with two, and (d) tricyclic with only one olefine linking. A clue as to which of these groups a given compound belongs can be obtained by a study of the number of hydrogen atoms it can take up when catalytically reduced and also from a study of its molecular refraction as for a hydrocarbon,  $C_{15}H_{24}$ , the values vary from 69.6 for an open-chain compound to 64.4 for a tricyclic system. Attention must, however, be paid to the exaltation of the refraction produced by conjugate double bonds and by semicyclic bonds (Chap. LXXI, H3).

1. **Open-chain compounds.**—**Nerolidol**,  $C_{15}H_{25} \cdot OH$ , occurs in orange flowers and Peru bark, and its structure as 2 : 6 : 10-trimethyl- $\Delta^{2:6:11}$ -dodecatriene-10-ol, I, or the isomeric  $\Delta^{1:6:11}$ -compound,



has been established by its synthesis from geranyl chloride, which reacts with ethyl acetoacetate yielding dihydropseudoionone (II), and this condensed with acetylene in presence of sodamide yields dehydronerolidol (III), which can be reduced by sodium and moist ether to nerolidol (IV).



Closely allied to and isomeric with nerolidol is **farnesol**, obtained from the flowers of *Acacia farnesiana* and other species of *Acacia*. The fact that treatment with acetic anhydride converts it into nerolidol (together with some **farnesene**), just as linalool is converted into nerol, suggests that it bears the same relationship to nerolidol that linalool does to nerol, and is therefore  $\text{Ger} \cdot CH_2 \cdot CMe : CH \cdot CH_2 \cdot OH$ , and this structure is confirmed by the fact that it is readily oxidized to the corre-

\* *Ger* stands for the geranyl group  $CMe_2 : CH \cdot CH_2 \cdot CH_2 \cdot CMe : CH \cdot CH_2$ , or  $CH_2 : CMe \cdot [CH_2]_3 \cdot CMe : CH \cdot CH_2$  (cf. this Chap., A.).

sponding aldehyde, **farnesal**, and the oxime of this when dehydrated yields a nitrile which on hydrolysis gives dihydropseudo-ionone (p. 992, O and H<sub>2</sub> adding on to olefine linking and producing fission).

**2. Monocyclic sesquiterpenes and alcohols.**—**Bisaboline**, C<sub>15</sub>H<sub>24</sub>, is very common in essential oils; it has b.-pt. 133°/12 mm., forms a trihydrochloride, m.-pt. 79°, and on ozonolysis gives acetone, lævulic acid and some succinic acid, but no formaldehyde or formic acid. When hydrogenated with platinum black as catalyst and in cyclohexane solution it yields a tetrahydro product with one olefine link in the chain, and as this on ozonolysis gives 4-methyl-cyclohexanone and 5-methylheptan-2-one, it must be a derivative of methyl-cyclohexane with a semicyclic olefine link, and as it is derived from  $\alpha$ -bisabolol it must be  $\Delta^1$ -tetrahydro-toluene with a para :CMe·CH<sub>2</sub>·CH<sub>2</sub>·CH:CMe<sub>2</sub> (side chain).

The alcohol,  $\alpha$ -**Bisabolol**, C<sub>15</sub>H<sub>25</sub>·OH, obtained as its acetate from farnesene by the action of acetic and sulphuric acids, is  $\Delta^1$ -tetrahydro-toluene with the ·CMe(OH)·CH<sub>2</sub>·CH<sub>2</sub>·CH:CMe<sub>2</sub> group in position 4, ring closure having taken place under the influence of the acids.

**Zingiberene**, C<sub>15</sub>H<sub>24</sub>, obtained from oil of ginger, is always contaminated with small amounts of bisabolene and on ozonolysis yields the same products as the latter, but differs in readily forming a dihydride and in reacting readily with ethyl diazoacetate. It contains three olefine linkings, as it can take up six atoms of hydrogen by catalytic reduction, and should therefore be a monocyclic compound, and its relatively high molecular refraction can be accounted for if two of the three linkings are conjugate. Treated with hydrogen chloride it yields a dihydrochloride from which **isozingiberene** can be isolated by treatment with alkali. Both the hydrocarbons yield cadalene when dehydrogenated with sulphur, but zingiberene catalytically dehydrogenated with palladium yields 2-methyl-6-*p*-tolyl-heptane, and this on oxidation gives terephthalic acid and no other acid, thus indicating that it is a *p*-disubstituted derivative of a reduced benzene. Its reactions point to zingiberene being a  $\Delta^1$ -tetrahydrotoluene with the group ·CHMe·CH:CH·CH:CMe<sub>2</sub> in position 4, and isozingiberene is probably 1:7-dimethyl-4-isopropyl- $\Delta^{3:6}$ -hexahydro-naphthalene. It also forms a tetrabromide.

**3. Dicyclic sesquiterpenes.**—These have been studied in

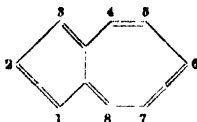
great detail and most of them contain a reduced naphthalene skeleton. The presence of this skeleton in **cadinene** from oil of cubebs, cade oil and juniper wood, was rendered highly probable when *Ruzicka* (1921, 505; 1922, 369) obtained **cadalene** by heating cadinene with sulphur and so removing hydrogen sulphide (*Vesterberg's* method), and then by synthesis proved cadalene to be 1:7-dimethyl-4-isopropyl-naphthalene. The starting-point in this synthesis is *p*-cymyl-2-acetic acid (1-methyl-4-isopropyl-benzene-2-acetic acid,  $C_3H_7 \cdot C_6H_3Me \cdot CH_2 \cdot CO_2H$ ); when reduced by *Bouveault's* method it yields the corresponding primary alcohol,  $\cdot CH_2 \cdot CH_2 \cdot OH$ , the bromide of which condenses with sodio-methylmalonic ester yielding  $\cdot CH_2 \cdot CH_2 \cdot CMe(CO_2Et)_2$ , and from this by hydrolysis and elimination of carbon dioxide the monobasic acid,  $\cdot CH_2 \cdot CH_2 \cdot CHMe \cdot CO_2H$ , is formed. The chloride of this acid with aluminium chloride (*Friedel-Crafts' reaction*) undergoes internal condensation, the second ring is formed and the product, 1:7-dimethyl-4-isopropyl-naphthalene, is identical with cadalene. Among the oxidation products of cadinene are benzene-1:2:4-tri- and benzene-1:2:3:4-tetra-carboxylic acids formed by the rupture of one or other of the two nuclei in the skeleton. Cadinene forms a dihydrochloride and contains two olefine bonds; they are undoubtedly in the rings and not in side chains, and according to *Ruzicka* and *Stoll* (1924, 94) ordinary cadinene is probably a mixture of the  $\Delta^{3:6}$ - and  $\Delta^{3:7}$ -1:7-dimethyl-4-isopropylhexahydronaphthalene (see also *Henderson and Robertson*, J. C. S., 1926, 2811).

**Eudesmol**,  $C_{15}H_{25} \cdot OH$ , m.-pt.  $82^\circ - 83^\circ$ , from eucalyptus oil and **selinene**,  $C_{15}H_{24}$ , from celery-seed oil, when heated with sulphur according to *Vesterberg's* method, yield not only hydrogen sulphide but also methyl sulphide, by the loss of one of the original methyl groups, and hence one of the methyl groups is attached to a tertiary C atom, probably a C atom common to two rings (cf. Chap. XLIX, C.), i.e. No. 5 or 10. The other product of dehydrogenation is 6-methyl-4-isopropyl-naphthalene (eudalene), the structure of which again has been proved by direct synthesis. The formula given by *Ruzicka* and *Capato* for eudesmol is 1-methylene-5-methyl-8-isopropyl-8-hydroxy-decahydronaphthalene (A., 1927, 453, 62). The presence of the methylene group is proved by the formation of a ketonic group CO in position 1 after ozonolysis, and position 8 for the hydroxyl group is selected since dihydroeudesmol

(2H added to semicyclic linkage) on ozonolysis yields a ketone with CO in position 8.

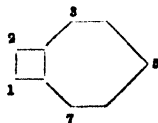
### TERPENES WITH A SEVEN-MEMBERED RING

Sesquiterpenes with a seven C ring have been described (Helv., 1936, 858; 1937, 224). They are the compounds which yield the blue colouring matters, azulenes, on dehydrogenation. The parent azulene has been synthesized and proved to be a condensed seven-carbon and five-carbon system,



and the azulenes obtained by dehydrogenation are the alkylated derivatives, e.g. 4:8-dimethyl-2-isopropyl- and 1:4-dimethyl-7-isopropyl-azulenes.

It has been suggested that  $\alpha$ -carophyllene from clove oil may contain a seven-membered ring condensed with a 4 carbon ring. It would have  $\text{Me}_2$  in either 1 or 2, an isopropenyl in 7, and a double link in 4 (C. and I., 1938, 123).

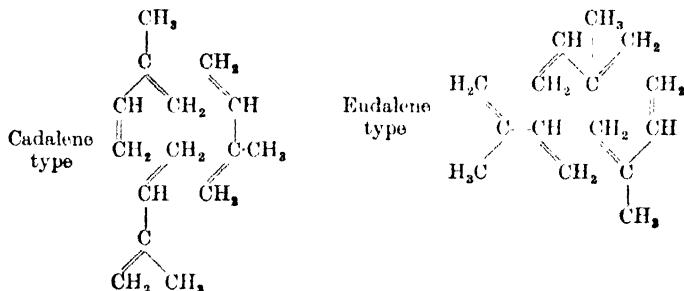


### G. Triterpenes

Several complex natural products are regarded as derived from the **triterpenes**,  $\text{C}_{30}\text{H}_{48}$  (cf. J. C. S., 1937, 989; 1938, 1233). Many on dehydrogenation give alkylated phenanthrenes.

The hydrocarbon **squalene**,  $\text{C}_{30}\text{H}_{50}$ , present in large amounts in the unsaponifiable fractions of certain fish oils (cf. Chap. LV, D1) is a dihydrotriterpene and is probably  $(\text{CMe}_2\text{:CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}\text{:CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CMe}\text{:CH}\cdot\text{CH}_2)_2$ , as it is one of the products formed by the action of activated magnesium on farnesyl bromide (this Chap., F.; cf. Helv., 1931, 78).

The structural formulæ for most of the terpenes and sesquiterpenes, whether of the open-chain, monocyclic or dicyclic types, are in complete harmony with the view that these compounds are polymerized isoprene, e.g.:



## LVIII. ALKALOIDS \*

For many years this group comprised all nitrogenous basic compounds derived from plant tissues, e.g. methylamine, betaine, asparagin, caffeine, but as the structures of such compounds were elucidated they were placed in their correct groups, and the alkaloids now include only those relatively complex cyclic bases containing the pyrrole, pyridine, quinoline, isoquinoline, phenanthrene and similar skeletons.

They form an extremely important group of compounds of pronounced physiological activity, and constitute the active principles of the common vegetable drugs and poisons.

With a single exception they occur exclusively in dicotyledons, and as a rule do not exist in the free state, but combined with organic acids in the form of salts. Such acids are malic (p. 283), citric (p. 298), and tannic (p. 528); quinic acid usually accompanies the alkaloids of opium.

A few of the alkaloids are built up of carbon, hydrogen, and nitrogen, e.g. coniine, nicotine. Such compounds as a rule are liquids and are readily volatile; the majority, on the other

\* *The Plant Alkaloids*, Henry, 3rd Edition, London, 1939. For early history cf. *Wuest*, C. and I., 1937, 1084.



hand, also contain oxygen, and then are usually crystalline and non-volatile. All are optically active, and as a rule lævoro-rotatory. A few like coniine are secondary bases, but the majority are tertiary, and a few are quaternary ammonium compounds.

The following reagents as a rule precipitate the alkaloids in the form of complex derivatives from solutions of their salts, viz. tannin, phosphomolybdic acid, a potassium iodide solution of iodine, and also potassium mercuric iodide. They are further characterized by their bitter astringent taste and by their poisonous properties. Each individual alkaloid gives characteristic colour reactions.

The alkaloids are usually extracted from plant tissues by lixiviating the finely-divided tissue with acidified water. The extract is then rendered alkaline with ammonia and the free alkaloid separated by filtration, or, if it is at all readily soluble, by extraction with chloroform.

Among the reactions made use of in elucidating the structure are:

1. Determination of the number of free hydroxyl groups by acetylation (cf. p. 233). Thus morphine can be shown to contain two, codeine one, and papaverine none.

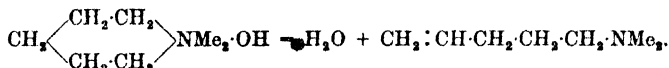
2. Determination of methoxy, OMe, groups by *Zeisel's* method or *Perkin's* modification. Determination of NMe, methylimino, groups by heating the hydriodide at 300° and estimating the CH<sub>3</sub>I eliminated (*Herzig and Meyer*).

3. Study of the action of hydrolysing agents. Esters are hydrolysed, but most other types of linking are resistant to such agents. Narcotine (p. 1008) yields opianic acid and hydrocotarnine, and is presumably an ester derived from these two compounds. Similarly, atropine (p. 1014) on hydrolysis yields tropic acid and tropine. As the products of hydrolysis are simpler than the original alkaloid, the elucidation of their constitutions is less difficult.

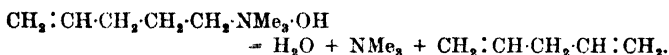
4. Examination of the products of oxidation. Thus codeine contains a secondary alcoholic group, as on oxidation it yields a ketone, codeinone, containing the same number of carbon atoms. Coniine when oxidized yields picolinic acid, and must thus be an  $\alpha$ -substituted derivative of pyridine. Cinchonine yields quinoline- $\gamma$ -carboxylic acid.

5. Determination of the primary, secondary, tertiary, or quaternary nature of the base.

6. Study of the degradation products obtained by exhaustive methylation. As an example of this method the simple secondary amine piperidine may be taken. When methylated by means of methyl iodide it yields first the tertiary amine methylpiperidine, and finally the quaternary ammonium iodide dimethylpiperidonium iodide. This with moist silver oxide yields the quaternary base, which on distillation decomposes into water and an unsaturated aliphatic tertiary amine:



When treated with methyl iodide and then with silver oxide this unsaturated base yields a quaternary hydroxide, which splits up into water, trimethylamine, and  $\Delta^{\alpha\delta}$ -pentadiene when distilled:

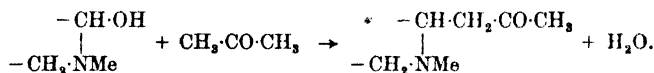


7. An examination of the products obtained by fusing the alkaloid with potash or by distilling it with zinc dust. Thus morphine and zinc dust yield phenanthrene together with other products, and hence the molecule of morphine probably contains a phenanthrene ring. Papaverine, when fused with potash, yields dimethoxy-iso-quinoline and 3:4-dimethoxy-toluene, and hence papaverine is probably an iso-quinoline derivative. The processes of fusion with potash and distillation with zinc dust require high temperatures, and as molecular rearrangements occur much more readily at high than at low temperatures, the conclusions drawn from a study of the products formed during such processes should be accepted with a certain amount of reserve unless supported by other evidence.

The alkaloids may be grouped according to their origin, e.g. the opium alkaloids, bases from solanine, &c., or according to the heterocyclic ring which they contain. The latter method is adopted here.

Many of the alkaloids are extremely complex, and several, e.g. quinine and strychnine, have so far not been synthesized in the laboratory. The function of such complex nitrogenous compounds in the plant system and the manner in which the complexes are built up in the tissue are problems which have

aroused much interest. *Robinson* in "A Theory of the Mechanism of the Phytochemical Synthesis of certain Alkaloids" (J. C. S., 1917, 876) has suggested probable methods of formation. The two main reactions which bring about union between carbon and carbon are (1) the aldol condensation (p. 154) of aldehydes, and (2) the condensation of an aldehyde or ketone with ammonia or an amine to a carbinol-amine,  $>C(OH) \cdot N<$ , and the reaction of this with substances containing the group  $>CH \cdot CO-$ , e.g.:



Reactions of this type require no condensing agent, and proceed almost to completion in aqueous solution at the ordinary temperature. The important starting-points are ammonia, formaldehyde, ornithine (arginine), and lysine (pp. 251 and 1211), and degradation products of carbohydrates, more particularly citric acid, which can give rise to acetone-dicarboxylic acid on oxidation, and this supplies the acetone complex.

Thus lysine,  $NH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$ , with formaldehyde undergoes methylation and oxidation, giving  $NHMe \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH:O$ , which with more formaldehyde

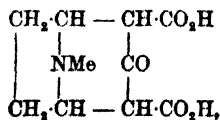
produces  $MeN \begin{array}{c} CH_2 - CH_2 \\ \diagdown \quad \diagup \\ CH(OH) \cdot CH_2 \end{array} CH_2$ , and this with acetone

yields  $MeN \begin{array}{c} CH_2 - CH_2 \\ \diagdown \quad \diagup \\ CH(CH_2 \cdot COMe) \cdot CH_2 \end{array} CH_2$ , the alkaloid methyl-

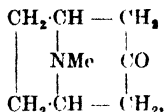
pelletierine of the pomegranate trees.

Similarly, tropinone (p. 1015) from 1:4-diaminovaleric acid (ornithine). By combined methylation and oxidation this can yield succindialdehyde and methylamine, which can undergo

condensation to  $\begin{array}{c} CH_2 \cdot CH(OH) \\ | \\ CH_2 \cdot CH(OH) \end{array} NMe$ . This product readily condenses with acetonedicarboxylic acid yielding:



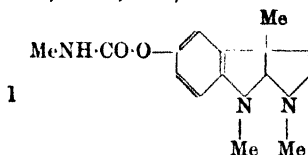
which by loss of carbon dioxide gives:



tropinone. By similar processes the formation of many alkaloids and derivatives of pyrrolidine, piperidine, quinoline, isoquinoline, related to the alkaloids, can be explained.

### A. Alkaloids with Condensed Pyrrole and Benzene Nuclei

**Phytostigmine** or **eserine**,  $\text{C}_{15}\text{H}_{21}\text{O}_2\text{N}_3$ , present in Calabar Beans, melts at  $105^\circ\text{--}106^\circ$ , has been shown by *Stedman* and *Barger* (J. C. S., 1925, 247) to have the structure I, i.e. one benzene and two N-methylpyrrolidine rings condensed. It is a ditertiary base, and is the ester formed from a phenolic OH and methylcarbamic acid. It has been synthesized by *Julian* and *Pikl* (J. A. C. S., 1935, 765):

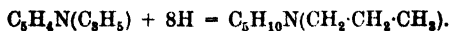


and has pronounced myopic properties due to its power to inhibit the hydrolysis of acetyl-cholin (Chap. LXVIII, B.) by cholin esterase. It resembles pilocarpin in producing powerful contraction of the intestine.

### B. Alkaloids derived from Pyridine

1. **Coniine**, dextro-rotatory *α-normal-propyl-piperidine*,  $\text{C}_8\text{H}_{10}\text{N}(\text{C}_3\text{H}_7)$ , is the poisonous principle of hemlock (*Conium maculatum*). It is a colourless dextro-rotatory liquid of stupefying odour, sparingly soluble in water, and boils at  $167^\circ$ . Hydriodic acid at a high temperature reduces it to normal octane, while nitric acid oxidizes it to butyric acid, and potassium permanganate to picolinic acid (hence the  $\alpha$ -position).

*Ladenburg* has prepared it synthetically by reducing  $\alpha$ -allylpyridine (p. 687) with sodium and alcohol:



The pyridine ring is reduced to a piperidine ring, and the unsaturated allyl side-chain is reduced to an *n*-propyl group. The  $\alpha$ -carbon atom is an asymmetric carbon atom, and hence the whole molecule is dissymmetric. The synthetical product is optically inactive, but it has been resolved by fractional crystallization of the *d*-tartrate. The relations of these two bases to one another and to the inactive modification are the same as those of *d*-, *l*- and *dl*-lactic acids.

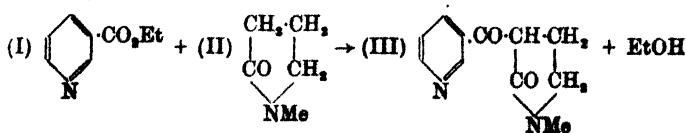
2. Alkaloids derived from pyridine are present in areca nut; these are **guvacine**, or 1:2:5:6-tetrahydropyridine-3-carboxylic acid, which has been synthesized by *Wohl* and *Losanitsch*, 1908; **guvacoline**, the corresponding methyl ester; **arecaine**, or arecaidine, the N-methyl derivative of guvacine; and **arecoline**, the methyl ester of arecaidine (B., 1919, 206).

3. **Ricine**,  $\text{C}_8\text{H}_8\text{O}_2\text{N}_2$ , an alkaloid from the castor-bean, is 1-methyl-2-keto-3-cyano-4-methoxy- $\Delta^1$ -dihydropyridine and has been synthesized by *Späth* and *Koller* (B., 1923, 2454).

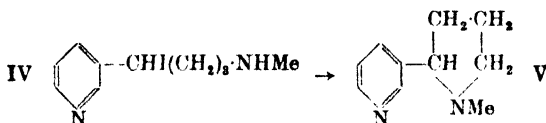
4. **Nicotine**,  $\text{C}_{10}\text{H}_{14}\text{N}_2$ , is the poisonous constituent of the tobacco plant, in which it exists in combination with malic and citric acids. It is a colourless, oily liquid soluble in water, and is lævo-rotatory. It has b.-pt.  $247^\circ$  and rapidly oxidizes in contact with the air. It is a di-tertiary base, as it combines with methyl iodide, yielding two isomeric quaternary salts. On oxidation with permanganate it yields nicotinic acid, and hence must be a  $\beta$ -pyridine derivative. These reactions, combined with its synthesis (*Pictet*, C. R., 1903, 137, 860), prove it to be  $\alpha$ -pyridyl-N-methyl-pyrrolidine (Formula V).

*Pictet's* synthesis is of historical interest, but involves the use of high temperatures, and hence details of structure must be accepted with reserve.

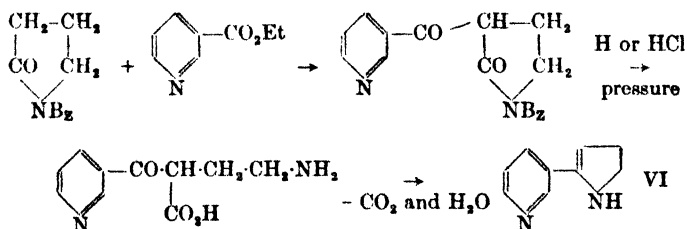
A simpler synthesis by *Späth* and *Bretschneider* (B., 1928, 327) is as follows: Ethyl pyridine-3-carboxylate (ethyl nicotinate) (I):



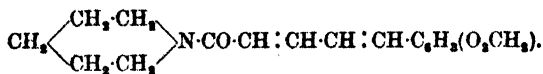
condenses with 1-methyl-2-pyrrolidone (II) in the presence of sodium ethoxide yielding the compound III, which with fuming hydrochloric acid yields the aminoketone  $C_5H_4N \cdot CO \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NHMe$  by hydrolysis and loss of  $CO_2$ . The ketone reduced with zinc dust and alkali yields the corresponding secondary alcohol, and this reacts with fuming hydriodic acid yielding the iodide (IV), from which *dl*-nicotine is formed by the action of alkalis entailing the loss of hydrogen iodide and the closing of the pyrrolidine ring.



5. **Myosmine**,  $C_9H_{10}N_2$ , is also present in tobacco and has been synthesized; it is a pyridyl- $\alpha$ -dihydropyrrole (VI). The synthesis is as follows:



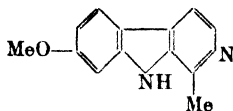
6. **Piperine** (p. 688), piperic acid piperidide, can be synthesized from piperoyl chloride and piperidine. It melts at  $128^\circ$ , is present in the fruits of different species of pepper, and on hydrolysis yields piperidine and piperic acid (p. 533).



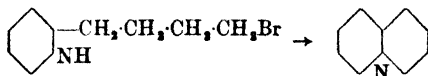
For synthesis of piperic acid see *Ladenburg and Scholtz*, B., 1894, 1958.

7. The alkaloid **harmine**, from the seeds of *Peganum harmala*, according to *Perkin and Robinson* (J. C. S., 1919, 933, 971;

1921, 1602; 1922, 1872), contains condensed benzene, pyrrole and pyridine nuclei and is represented by the formula:



8. **Norlupinane**,  $C_9H_{17}N$ , a degradation product of lupinine, an alkaloid from lupin seeds (*Clemons* and others, J. C. S., 1931, 437, 3190), has been synthesized by ring closure of 1- $\omega$ -bromobutyl-piperidine (*ibid.* 1935, 1743):



### C. Bases derived from Quinoline

Among these are the alkaloids present in **Cinchona** barks.

(a) **Quinine**,  $C_{20}H_{24}O_2N_2 + 3H_2O$ , a diacid base of intensely bitter taste and alkaline reaction, of which the sulphate and chloride are universally used as febrifuges. It crystallizes in prisms or silky glistening needles, melts at  $177^\circ$  when anhydrous, is sparingly soluble in water, and is lævo-rotatory. Dilute solutions of its salts show a brilliant blue fluorescence.

As a base quinine is a tertiary diamine, but it contains in addition—as its reactions show—one hydroxy-, one methoxy-group and an ethylene linking, and seems to be built up of two different ring systems:



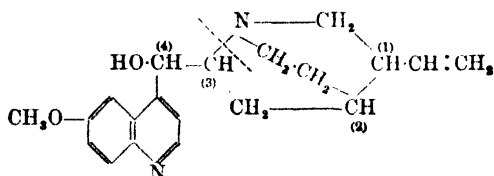
The first of these represents the radical of a 6-methoxyquinoline, and this compound is obtained when quinine is fused with potash. The second system probably possesses a ring similar to that of tropine, since it yields as decomposition products sometimes a pyridine derivative (e.g.  $\beta$ -ethyl-pyridine on fusion with alkali), and sometimes benzene derivatives containing no nitrogen (e.g. a phenolic compound,  $C_{10}H_{12}OH$ , together with ammonia, on successive treatment with phosphorus pentachloride, potash, and hydrobromic acid).

It yields quinic acid, 6-methoxyquinoline-4-carboxylic acid,

$C_9H_5N(OCH_3)CO_2H$  (p. 696), and meroquinene when oxidized with dichromate mixture.

Meroquinene appears to be 3-vinylpiperidyl-4-acetic acid (B., 1897, 1326),  $CO_2H \cdot CH_2 \cdot CH \begin{matrix} \swarrow CH(CH:CH_2) \cdot CH_2 \\ \searrow CH_2 \text{---} CH_2 \end{matrix} \rangle NH$ , as it yields first cincholoiponic acid (3-carboxypiperidyl-4-acetic acid), and finally *loiponic acid* (piperidine-3:4-dicarboxylic acid), when oxidized with permanganate.

The formula for quinine is that of combined quinoline and quinuclidine nuclei (*Rabe*)



Both quinine and cinchonine when oxidized yield ketones containing the same number of C atoms. When heated with acetic acid the two alkaloids yield isomeric products known respectively as *quinotoxine* and *cinchotoxine* on account of their poisonous properties. These bases are ketones and secondary bases, and are formed by the conversion of the  $CH(OH)$  group into  $CO$  and the rupture between the N atom and the C atom of the adjacent CH group, as indicated by the dotted line. Hydroquinine has been synthesized by *Rabe* and others (B., 1919, 1842; 1931, 2487).

Quinine is a valuable drug in cases of malaria; numerous substitutes are now employed, especially quinine derivatives devoid of bitter taste. The esters derived from the alcoholic OH group—*aristoquinine*, diquinine carbonate; *euquinine*, ethyl quinine carbonate; and *salokinine*, quinine salicylate—are used (cf. LXV, K.).

The molecule of quinine contains four centres of dissymmetry, viz. the carbon atoms numbered 1 to 4 in the formula, hence several stereo-isomeric forms are possible; one of these is the alkaloid *d*-quinidine which occurs in opium. The four known forms are quinine, epiquinine, quinidine and epiquinidine, with the melting-points  $177^\circ$ , oil,  $168^\circ$  and  $113^\circ$ . The last three are dextrorotatory, whereas quinine is lævo. According to *Rabe* (A., 1932, 492, 242) the optical signs of carbon atoms



3 and 4 are respectively --, -+, ++ and +- in the four forms. On the other hand, in all the natural opium alkaloids carbon atom 3 has the same signs as 4, viz. quinine, quinidine, cinchonine and cinchonidine.

(b) **Cinchonine**,  $C_{19}H_{22}ON_2$ , is similar to quinine, but without the methoxy group in the quinoline nucleus. It crystallizes in colourless prisms, sublimes readily, and is not so active a febrifuge as quinine. When oxidized with dichromate and sulphuric acid it yields cinchoninic (quinoline-4-carboxylic) acid and meroquinene; with permanganate it yields cinchotenine and carbonic acid. Cinchotenine no longer combines with hydrogen chloride, and in the oxidation the double linking present in cinchonine has been removed and a carboxylic group introduced. When treated with  $PCl_5$  and then with alcoholic potash, cinchonine loses a molecule of water, yielding *cinchene*,  $C_{19}H_{20}N_2$ , which can be hydrolysed by 25 per cent phosphoric acid to lepidine (4-methyl-quinoline) and meroquinene. It has very little therapeutic value.

These are but a few of the numerous alkaloids present in these barks. In addition, organic acids (e.g. quinic and quino-tannic) and neutral substances are also present.

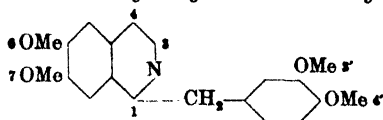
## D. Bases derived from *iso*-Quinoline

1. **Papaverine**,  $C_{20}H_{21}O_4N$  (*Merck*, 1848), is found (1 per cent) together with narcotine, narceine, laudanoline, laudanine, and the morphine alkaloids in opium,\* the solid obtained by drying the juices extracted from the unripe seed vessels of *Papaver somniferum*. In addition to some twenty alkaloids, many of which are present in only small quantities, opium also contains fats, resins, sugars, albumins, &c. The alkaloid crystallizes in prisms, m.-pt.  $147^\circ$ , and is optically inactive. It has hypnotic properties, but not to the same extent as morphine. It is a tertiary base, and all four oxygen atoms are present as methoxy groups, and when hydrolysed with hydriodic acid the corresponding tetrahydroxy-derivative, *papaveroline*,  $C_{18}H_{19}O_4N$ , is formed. When oxidized with permanganate it yields first *papaveraldine*,  $C_{20}H_{19}O_5N$ , and finally 6:7-dimethoxy-*iso*-quinoline-carboxylic acid and  $\alpha$ -carbo-cinchomeronic acid (pyridine-2:3:4-tricarboxylic acid). When

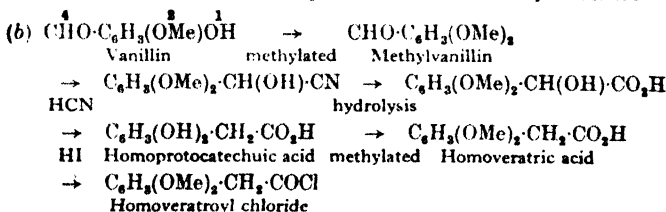
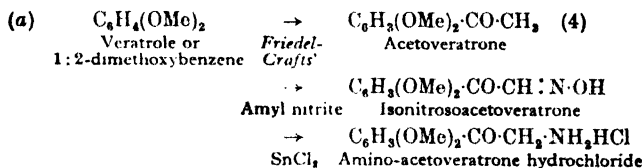
\* *Opium*, J. R. Nichols, Inst. C. Lecture, 1938.

fused with potash it takes up two hydrogen atoms, and yields 6 : 7-dimethoxy-iso-quinoline and 3 : 4-dimethoxy-toluene. When reduced, the N ring adds on 4 H atoms.

From these and other reactions *G. Goldschmidt* concluded that the base is 3' : 4'-dimethoxybenzyl-6 : 7-dimethoxy-iso-quinoline:



and this formula has been confirmed by *Pictet* and *Gams'* synthesis (C. R., 1909, 149, 210) by the following steps:



(c) Amino-acetoveratrone hydrochloride and homoveratroyl chloride condense in the presence of cold potassium hydroxide, yielding  $(\text{OMe})_2\text{C}_6\text{H}_3\text{CO}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{C}_6\text{H}_3(\text{OMe})_2$ ; this can be reduced to the corresponding secondary alcohol which reacts with dehydrating agents, losing two molecules of water and forming 3' : 4'-dimethoxybenzyl-6 : 7-dimethoxy-iso-quinoline, which is identical with papaverine.

2. **Laudanosine**,  $\text{C}_{21}\text{H}_{27}\text{O}_4\text{N}$ , crystallizes in needles, m.-pt.  $89^\circ$ , and is dextro-rotatory. It has been shown by *Pictet* and *Athanescu* (B., 1900, 2346) to be an N-methyl-tetra-hydropapaverine, and has been synthesized by *Pictet* and *Finkelstein* (C. R., 1909, 148, 295).

3. **Laudanine** is the 3-hydroxy-4-methoxybenzyl compound corresponding with laudanosine (3 : 4-dimethoxybenzyl-) (M., 1921, 273).

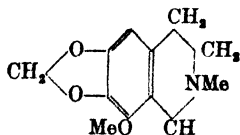
4. **Hydrocotarnine**, obtained from opium, but probably formed from other alkaloids during extraction, is N-methyl-6:7-methylenedioxy-tetrahydro-isoquinoline (Formula II, below). Cotarnine, on the other hand, is 4:5-methylenedioxy-benzaldehyde with the group  $\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NHMe}$  in position 2 and readily forms hydrocotarnine by internal condensation.

5. **Narceine** (*Pelletier*, 1832), also present in opium, is cotarnine with  $\cdot\text{CH}_2\cdot\text{CO}\cdot\text{C}_6\text{H}_2(\text{OMe})_2\cdot\text{CO}_2\text{H}$  in place of  $\cdot\text{CHO}$  and  $\text{NMe}_2$  in place of  $\cdot\text{NHMe}$ .

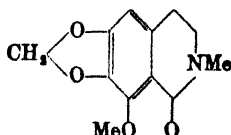
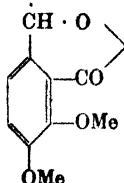
6. **Narcotine**,  $\text{C}_{22}\text{H}_{23}\text{O}_7\text{N}$ , occurs in opium (6 per cent), crystallizes in colourless needles, m.-pt.  $176^\circ$ , and is lævoro-rotatory. It is a feeble tertiary base, and its salts are readily hydrolysed by water. It contains three methoxy groups, and when hydrolysed by dilute acids or alkalis yields opianic acid and hydrocotarnine. When reduced it yields meconine and hydrocotarnine, and when oxidized yields opianic acid and cotarnine, and when heated with alkalis at  $220^\circ$  yields methylamines, thus indicating that the N-atom is methylated (Formula I).

The *dl*-compound (called **gnoscopine**) has been synthesized in small quantities (*Perkin and Robinson*, J. C. S., 1911, 776) by boiling an alcoholic solution of cotarnine and meconine, and has been resolved by means of *d*-bromo-camphor-sulphonic acid.

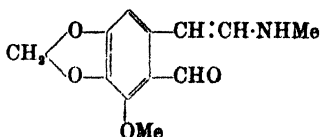
## II Hydrocotarnine,



I Narcotine,



III Cotarnine,



Both meconine (VI, p. 1009), the lactone of 6-hydroxymethyl-2:3-dimethoxybenzoic acid, and cotarnine have been synthesized. The former by *Fritsch* (A., 301, 352) and the latter by

*Salway* (J. C. S., 1910, 1208), and also by *Decker* and *Becker* (A., 1913, 395, 328).

The structural formula III or a cyclic structure corresponding with hydrocotarnine was deduced by *Roser* for cotarnine by a study of its degradation products. When methylated and decomposed by alkalis it yields trimethylamine and an aldehyde, cotarnone,  $C_9H_9O_3 \cdot CHO$ , which on further oxidation gives a methoxy-dibasic acid, known as cotarnic acid, and this with hydriodic acid and phosphorus at  $160^\circ$  yields gallic acid (3 : 4 : 5-trihydroxybenzoic acid).

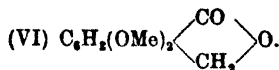
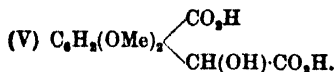
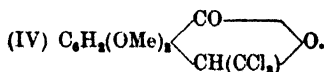
Cotarnic acid is 3-methoxy-4 : 5-methylenedioxyphthalic acid, and cotarnone 6-vinyl-3-methoxy-4 : 5-methylenedioxybenzaldehyde.

The steps in *Salway's* synthesis of cotarnine are: Myristic aldehyde (3-methoxy-4 : 5-methylenedioxy-benzaldehyde)  $\rightarrow$  3-methoxy-4 : 5-methylenedioxy-cinnamic acid  $\xrightarrow{\text{Perkin's synthesis}}$  corresponding dihydro acid  $\rightarrow$  acid amide  $\xrightarrow{\text{red}}$   $\beta$ -3-methoxy-4 : 5-methylenedioxy-phenylethylamine  $\xrightarrow{\text{Hofmann reaction}}$  phenacetyl-derivative of amine  $\rightarrow$  8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro-isoquinoline  $\rightarrow$  benzylhydrocotarnine  $\rightarrow$  cotarnine.

Methochloride  
with tin and HCl

$H_2SO_4$   
+  $MnO_2$

*Fritsch's* synthesis of meconine consists in condensing chloral with the ester of 2 : 3-dimethoxybenzoic acid, hydrolysing the product (IV) to the hydroxy dibasic acid (V), and, finally, eliminating  $CO_2$  and  $H_2O$  by heating the dibasic acid and obtaining the lactone, meconine (VI):



7. **Hydrastine**,  $C_{21}H_{21}O_6N$ , occurs in the roots of *Hydrastis canadensis*, and differs from narcotine by having no methoxy group in the iso-quinoline ring. When oxidized it yields opianic acid and hydrastinine, which is the analogue of cotarnine (synthesis of hydrastinine, cf. *Fritsch*, A., 1895, 286, 18).

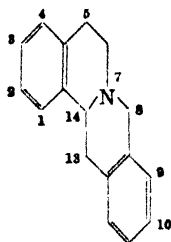
8. **Emetine**, cephaeline monomethyl ether,  $C_{29}H_{40}O_4N_2$ , and cephaeline are alkaloids present in ipecacuanha, and appear

to be derived from iso-quinoline, as 6 : 7-dimethoxy-iso-quinoline-1-carboxylic acid is found among their oxidation products. The former is largely used for the cure of amœbic dysentery. For structure see *Brindley-Pyman* (J. C. S., 1927, 1067).

For absorption spectra of iso-quinoline alkaloids cf. *Dobbie and Fox*, J. C. S., 1914, 1639.

### E. Bases with two Condensed iso-Quinoline Residues

1. The alkaloids from *Berberis vulgaris* and *Calumba root* (*Jateorhiza Calumba*) from East Africa are derivatives of condensed iso-quinoline residues with the skeleton:



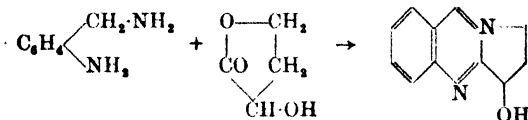
Three bases are: (1) **Palmatine** with four methoxy groups in positions 2 : 3 : 9 : 10. (2) **Jatrorrhizine** with a free hydroxyl in position 1, in addition to the four methoxy groups. (3) **Columbamine** isomeric with (2) has the free hydroxyl in position 2. All three have a double link between carbons numbered 13 and 14 and also between N (7) and carbon numbered 8, so that they are ammonium bases. Closely related is **Berberine**, from *Hydrastis canadensis*, which has  $O_2CH_3$  in place of the two methoxy groups in positions 2 and 3 in palmatine. It is readily converted into the latter by hydrolysing to the tetrahydroxy compound and then methylating (B., 1925, 2267). The structure of these bases was determined by *Feist* and *Sandstedt*, Arch. Pharm., 1918, 2561, and *Späth* and *Durchinsky* (B., 1925, 1939; 1927, 383). For synthesis of tetrahydroberberine cf. J. C. S., 1925, 740; 1927, 548.

2. **Corydaline**,  $C_{23}H_{27}O_4N$ , from *Corydalis cava*, crystallizes in prisms, m.-pt.  $134.5^\circ$ , and contains four methoxy groups.

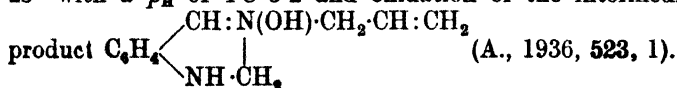
The formula given below by *Koeppli* and *Perkin* (J. C. S., 1928, 2989) differs slightly from that suggested by *Dobbie* and *Lauder* (1903, 605), and represents it with the skeleton given above, with the methoxy groups in positions 2:3:9:10 and a methyl group at 13, but no double link between 13 and 14.

### F. Bases with a Benzene, a Pyrimidine and a Pyrrolidine Ring

**Peganine** or **vasicine**,  $C_{11}H_{12}ON_2$ , from *Peganum harmala*, is laevo-rotatory, and is readily synthesized by condensing *o*-aminobenzylamine with  $\gamma$ -lactone of 2:4-dihydroxybutyric acid at  $200^\circ$  (B., 1936, 255).

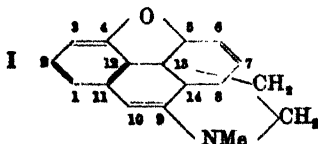


The same base can also be prepared by the condensation of *o*-aminobenzaldehyde, allylamine and formaldehyde at  $25^\circ$  with a  $p_H$  of 4.8-5.2 and oxidation of the intermediate



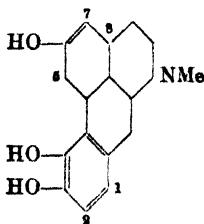
### G. Bases from Phenanthrene

The alkaloids morphine, codeine, thebaine and neopine are characterized by containing a phenanthrene nucleus in addition to a nitrogen ring, as in structure I. Where the phenanthrene skeleton is represented by C atoms 1-10, in addition there is an oxygen bridge between C atoms 4 and 5 and a  $\text{CH}_2\text{CH}_2\text{NMe}$  between carbons 13 and 9 with the N attached to No 9. The skeleton thus contains a reduced iso-quinoline ring in addition to the phenanthrene structure.



Morphine has two OH groups in positions 3 and 6, and a double link in 6:7. Codeine is morphine monomethyl ether with OMe in position 3, and neopine is the isomeric monomethyl ether with OMe in position 3, and a double bond in position 8:14 (*Robinson* and others, J. C. S., 1926, 903), and thebaine is morphine dimethyl ether.

1. **Morphine** (*Sertürner*, 1805),  $C_{17}H_{19}O_3N$ , constitutes on the average 10 per cent of opium. It crystallizes in small prisms ( $+H_2O$ ), melting and decomposing at  $230^\circ$ , has a bitter taste, and is a valuable soporific. It is a mono-acid tertiary base, containing two hydroxyl groups, one of which is phenolic and the second alcoholic. When distilled with zinc dust it yields phenanthrene together with pyrrole, pyridine, and trimethylamine. Further proof of the presence of the phenanthrene nucleus has been afforded by the process of exhaustive methylation. With methyl iodide it yields codeine methiodide, formed by the methylation of the phenolic hydroxyl group and addition of methyl iodide to the tertiary N-atom. This product, with potassium hydroxide, loses hydrogen iodide and yields a tertiary base, *methylmorphimethine*, which with acetic anhydride gives 3-methoxy-4-hydroxy-phenanthrene (methylmorphol) and hydroxyethyldimethylamine,  $OH \cdot CH_2 \cdot CH_2 \cdot NMe_2$ . The constitutional formula given above is due to *Gulland* and *Robinson* (J. C. S., 1923, 980, cf. also 1926, 909), and *Mem. Man. P. S.*, 1925), who give evidence for the double bond in position 6:7. Hydrochloric acid at  $140^\circ$ – $150^\circ$  converts morphine into **apomorphine**; the change is accompanied by the fission of the O ring and the formation of OH in position 4, and also the change in the  $\cdot CH_2 \cdot CH_2 \cdot NMe \cdot$  bridge, so that the  $CH_2$  end becomes attached to C atom No. 8 instead of 13.



For general discussion cf. *Fieser*, "Natural Products related to Phenanthrene", 1936.

2. **Codeine**,  $C_{18}H_{21}O_3N$ , is a methyl derivative of morphine,

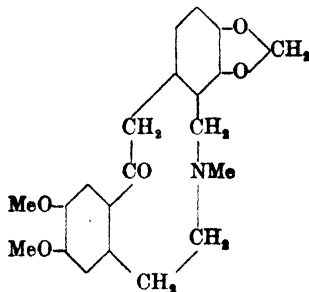
and can be obtained from the latter by methylation of its phenolic group. When oxidized it yields the ketone *codeinone*, and this with acetic anhydride yields hydroxyethyl-methylamine and 3-methoxy-4:6-dihydroxy-phenanthrene.

Numerous alkyl derivatives of morphine are manufactured and used as drugs in place of codeine. *Dionine* is ethylmorphine hydrochloride, *peronine* is benzylmorphine hydrochloride, *heroin* is diacetylmorphine.

For synthetical products allied to morphine see *Knorr*, A., 301, 1; 307, 171, 187; B., 1899, 732.

## H. Bases with a Ten-membered Ring

**Cryptopine**,  $C_{21}H_{23}O_5N$ , and **Protopine**,  $C_{20}H_{19}O_5N$ , are present in small amounts in opium, and *Perkin* (J. C. S., 1916, 815) suggests the formula containing a ten-membered ring ( $1N + 9C$ ) condensed with two benzene nuclei for cryptopine, which cannot be resolved into optically active modifications.



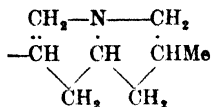
## I. Bases with a Cyclo-pentenophenanthrene Nucleus

Certain alkaloids from species of *solanum* when subjected to selenium dehydrogenation yield methyl-cyclopentenophenanthrene—*Diel's* hydrocarbon—and hence are closely allied to the sterols and bile acids (Chap. LXII).

The eyes and shoots of potatoes contain a glycoside *solanine*, which on hydrolysis yields the alkaloid *solanidine*,  $C_{27}H_{45}ON$ , to which *Clemo* and others (J. C. S., 1936, 1299) give a structure based on that of the sterols (Chap. LXII, A) with OH in



3, double link in 5 : 6, and the following side chain attached to C, No. 17:



The S. African winter cherry (*Solanum pseudocapsicum*) gives an alkaloid **solanocapsidine**,  $\text{C}_{26}\text{H}_{42}\text{O}_4\text{N}_2$ , which also gives *Diel's* hydrocarbon on dehydrogenation (*ibid.* 1537). For Solanidine, F, cf. B., 1936, 811.

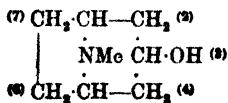
### J. Bases with Two Condensed Pyrrolidine Rings with —CH·NMe·CH— in common

Atropine and hyoscyamine are isomeric bases of the formula  $\text{C}_{17}\text{H}_{23}\text{O}_3\text{N}$ , which can be respectively prepared from *Atropa Belladonna* (Deadly Nightshade) and *Datura Stramonium*, and which are remarkable for their mydriatic action (power of dilating the pupil of the eye).

**Atropine** crystallizes in colourless prisms or needles melting at  $115^\circ$ , possesses an extremely bitter taste, is optically inactive, and is hydrolysed by baryta water to *dl*-tropic acid ( $\alpha$ -phenyl- $\beta$ -hydroxy-propionic acid,  $\text{OH}\cdot\text{CH}_2\cdot\text{CHPh}\cdot\text{CO}_2\text{H}$  p. 530), and tropine,  $\text{C}_8\text{H}_{15}\text{ON}$ , and is therefore the tropic ester of tropine. The alkaloid can be synthesized by evaporating a dilute hydrochloric acid solution of tropine and tropic acid. A complete synthesis of atropine has been accomplished, as both tropic acid and tropine have been synthesized.

When optically active (*d*- and *l*-) tropic acids are used, a dextro- and a lævo-rotatory atropine result). When other organic acids are employed in place of tropic acid, similar bases, the "**tropeines**", are obtained; thus mandelic acid yields **homatropine**,  $\text{C}_{10}\text{H}_{21}\text{NO}_3$ , which exerts, like atropine, a mydriatic action, although a less lasting one (*Ladenburg*, A., 217, 82; *Jovett and Pyman*, J. C. S., 1909, 1090).

Tropine itself is a cycloheptanol with a nitrogen bridge or two N-methylpyrrolidine rings condensed to give —CH·NMe·CH— in common:



(Willstätter, B., 1898, 1538, 2498, 2655). For synthesis cf. Willstätter, A., 1901, **317**, 307; B., 1901, 129, 3163.

It is a tertiary base, crystallizes in plates, m.-pt. 62° and b.-pt. 220°.

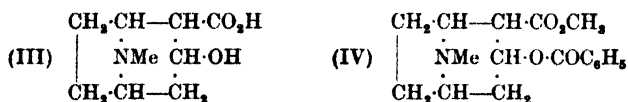
On oxidation it yields the ketone **tropinone** (I) and then **tropinic acid**, or 1-methyl-pyrrolidine-2-carboxylic-5-acetic acid. Concentrated hydrochloric acid converts it into **tropidine** (II),



an oily base distilling at 162°, and also obtainable by the elimination of carbon dioxide from anhydro-ecgonine.

Tropinone is readily synthesized from succindialdehyde, methylamine, and acetone, or calcium acetonedicarboxylate (Robinson, J. C. S., 1917, 762). For details see p. 1000. Tropine is formed when tropinone is reduced with zinc dust and concentrated acid. It exists in two forms, tropine and the more stable  $\psi$ -tropine, which are probably stereo-isomeric. In the one case the Me and OH (of the  $\text{CH}\cdot\text{OH}$  group) are on the same side of the plane of the ring and on the other the Me and H (of the  $\text{CH}\cdot\text{OH}$  group on the same side).

**Ecgonine**, or *tropine-carboxylic acid* (III),

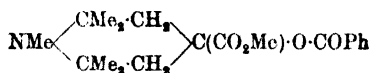


crystallizes with one molecule of water, and may be obtained by the hydrolysis of products contained in coca leaves. It melts at 198°, and is lævo-rotatory; and, on warming with alkalis, gives iso-ecgonine, which is dextro-rotatory. As an alcohol it forms a benzoyl derivative, and as an acid a methyl ester (see Cocaine). It is synthesized by the action of carbon dioxide on the metallic salts derived from tropinone (Willstätter and Bode, B., 1900, 411), and the reduction of the product with sodium amalgam in weakly alkaline solution.

**Cocaine**, or *benzoyl-l-ecgonine methyl ester* (IV) is the active constituent of the coca leaf (*Erythroxylon coca*); it melts at 98°, is lævo-rotatory, and is used in surgery as a local anæsthetic for deadening pain. It has been synthesized by benzoylating and esterifying ecgonine (B., 1885, 2953).

**Hyoscyamine**, which crystallizes in needles or plates, melting at  $109^{\circ}$ . It is the *l* form of atropine, and is readily racemized to this under the influence of various alkalis (*Will, B.*, 1888, 1725, 2777). In contact with water it is slowly hydrolysed to *l*-tropic acid and inactive tropine.

Various substitutes for cocaine have been recommended, as its solutions do not keep well. *Willstätter* (*B.*, 1896, 1575, 2216) obtained an isomeride of ecgonine by the addition of HCN to tropinone (1) and subsequent hydrolysis, and from this  $\alpha$ -cocaine was obtained by benzylation and esterification.  $\alpha$ -Cocaine contains both  $\text{CO}_2\text{Me}$  and  $\text{COPh}$  groups attached to the same carbon atom and has no anæsthetic properties.  $\alpha$ -**Eucaine** is a cheap substitute for cocaine prepared from triacetoneamine,  $\text{NH} \begin{array}{c} \diagup \text{CMe}_2\text{CH}_2 \\ \diagdown \text{CMe}_2\text{CH}_2 \end{array} \text{CO}$  (p. 159), by addition of HCN, hydrolysis, benzylation of the hydroxy acid thus formed, and final methylation of the imino and carboxylic groups. Its structure is:



(*Merling*, 1897). Although more stable and less toxic than cocaine, it produces irritant effects when injected, and is now replaced by other synthetic products (cf. Chap. LXV, I.).

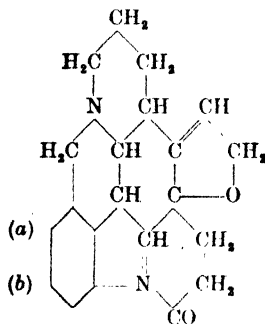
**Scopolamine** and **hyoscyne**, present in *Datura meteloides*, are the tropyl esters of scopoline,  $\text{C}_8\text{H}_{13}\text{O}_2\text{N}$ , and the former is the racemic form of the latter. Dihydroscopoline is related to tropine; it contains two hydroxyl groups in positions 6 and 7 and none in position 3. Scopoline is the cyclic ether with O uniting carbons 3 and 7, and is formed from an intermediate compound scopine (ether with O uniting carbons 6:7) by molecular rearrangement. Scopine is thus the 6:7 oxide of tropine, and is the first product formed on hydrolysing hyoscyne.

## K. Strychnine Bases

*Strychnos nux vomica* and certain other beans contain:

(a) **Strychnine**,  $\text{C}_{21}\text{H}_{22}\text{O}_2\text{N}_2$ . This is excessively poisonous, produces tetanic spasms, crystallizes in four-sided prisms,

and yields quinoline and indole when fused with potash,  $\beta$ -picoline when distilled with lime, and carbazole when heated with zinc dust. It is a mono-acid tertiary base, and melts at  $284^{\circ}$ . The formula suggested by *Fawcett, Perkin* and *Robinson*, J. C. S., 1928, 3082, is



(b) **Brucine**,  $C_{23}H_{26}O_4N_2 \cdot 4H_2O$ , which crystallizes in prisms, and is converted into homologues of pyridine on fusion with potash. It is a dimethoxystyrychnine with OMe in positions (a) and (b).

## LIX. SYNTHETIC DYES \*

Before *Perkin's* synthesis of the first aniline dye in 1856, the dyestuffs used in dye-houses belonged to the group of natural colours, and were prepared from vegetable and animal tissues, e.g. alizarin from madder, fustic from the sumach tree, cochineal from the cochineal insect, *Coccus cacti*, and lac dye as a by-product in the manufacture of lac from the lac insect, *Coccus lacca*. At the present time nine-tenths of the dyes used in the cotton, woollen, and other industries are of synthetic origin, and are derived from coal-tar. A few natural dyes are still used; the most important of these are the log-wood dyes, used for blacks on animal fibres, and substances of

\*Thorpe and Linstead, *Synthetic Dyestuffs*, London, 1933; F. M. Rowe, *The Development of the Chemistry of Commercial Synthetic Dyes* (1856-1938), Lecture Institute of Chemistry, 1938; Fierz-David, *Künstliche Farbstoffe*, 1935.

the type of anatto and turmeric, which are used for colouring foodstuffs. In two cases severe competition has occurred between the natural dye and the same dye produced synthetically; in the one case, alizarin, the synthetic product has completely replaced the natural dye, and in the other, indigo, the natural product has become replaced to such an extent that the area under cultivation has diminished enormously.

The number of artificial dyes is very large: in 1914 Germany produced about 900 different types of dyes; in 1936 the number was about 2000, half of which are azo-dyes. For complete list to 1924 cf. Colour Index of Society of Dyers and Colourists. Some of the simpler of these, such as azo-dyes, triphenylmethane dyes, and alizarin have been referred to in earlier chapters.

The extent of the synthetic dye industry can be gathered from the fact that in 1912 Germany produced dyestuffs to the value of £12,500,000, and that in the same year England used dyes to the value of £2,000,000, 90 per cent of which were imported. The total production in 1936 was 218,750 tons, of which Germany produced 74,000, U.S.A. 53,000, and Great Britain 27,000 tons. In the same year Great Britain imported to the value of 1.86 million pounds and exported to the value of 1.32 million pounds. The amounts produced in Great Britain have decreased since 1936.

The more important synthetic dyestuffs can be classified as follows:

- A. Nitroso- and nitro-dyestuffs.
- B. Azo-dyes.
- C. Stilbene, pyrazole, and thiazole dyestuffs.
- D. Di- and triphenylmethane dyes.
- E. Xanthene dyestuffs.
- F. Acridine and Quinoline dyestuffs.
- G. Indamine and Indophenol dyestuffs.
- H. Azines, Oxazines, and Thiazines.
- I. Hydroxy-Ketone dyestuffs.
- J. Sulphide dyes.
- K. Vat dyestuffs: Indigo and Indanthrenes.
- L. Phthalo-cyanins.

The grouping is based on chemical relationships rather than on any similarities in dyeing properties.

## A. Nitroso- and Nitro-dyestuffs

A good mordant dye is produced by the introduction of one or more hydroxyl groups into the molecule of an aromatic nitroso derivative, the chromophore being the nitroso group and at least one OH in the *ortho*-position. Examples are: **Resorcine Green**, 2:3:6-trihydroxynitrosobenzene; **Fast Green O**, dinitroso-resorcinol; the three **gambines**, R = 1-hydroxy-2-nitroso-, Y = 1-nitroso-2-hydroxy-, and B = 1-nitroso-2:7-dihydroxy-naphthalene. They are generally used with an iron (ferrous) mordant forming green lakes. They are typical tautomeric substances, viz. *o*-nitrosophenol  $\rightleftharpoons$  *o*-quinone monoxime.

Examples of nitro-dyestuffs are: Picric acid (p. 480), salts of 2:4-dinitro-1-naphthol or *Martius* yellow, and the commoner naphthol yellow S or sodium 2:4-dinitro-1-naphthol-7-sulphonate (p. 574).

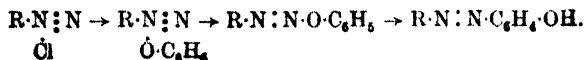
A more complex nitro-dye is **Polar Yellow Brown**,  $p\text{-C}_6\text{H}_4\cdot[\text{NH}\cdot\text{C}_6\text{H}_3(\text{SO}_3\text{Na})\cdot\text{NH}\cdot\text{C}_6\text{H}_3(\text{NO}_2)_2]_2$ , best obtained by condensing 2 mols. of *p*-nitrochlorobenzene-*o*-sulphonic acid with *p*-phenylenediamine, reducing the  $\text{NO}_2$  to  $\text{NH}_2$ , and then condensing with 2 mols. of 2:4-dinitrochlorobenzene.

## B. Azo-dyestuffs

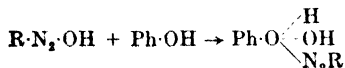
The common method of preparing azo-dyes is by coupling a diazonium salt with a secondary component, e.g. a phenol or an amine, but a few are prepared by other methods. Diazotization of the base is rendered difficult by negative groups adjacent to the amino group, e.g. *o*-nitraniline, and negative groups in the secondary component diminish the rate of coupling (*Meyer*, B., 1914, 1741). The introduction of a *p*-nitro group into the amine yields a diazonium salt which couples readily.

Several views have been expressed regarding the mechanism of coupling:

1. *Dimroth* (1907) suggests that with the alkali salt of a phenol the reaction is:



2. *Auwers* and *Michaelis* suggest the formation of an oxonium (or ammonium salt) which gives the dye on elimination of water and rearrangement (B., 1914, 1286, cf. *Karrer*, 1915, 1398):



3. As diazonium salts react with butadienes and with mesitylene, *Meyer* (1919, 1488; 1921, 2265) claims that amino and hydroxy groups are not essential, and suggests the addition of the diazonium hydroxide to a conjugated chain of carbon atoms.

### 1. MONOAZO DYESTUFFS

The coupling of the diazonium salt with an alkaline solution of a phenol takes place more readily than with an acid solution of an amine. In the former case, however, a large excess of caustic soda has to be avoided, as this tends to transform the diazonium salt into an isodiazohydroxide (p. 453), which does not couple with the phenol. The usual practice is to add sufficient caustic soda solution to the phenol to transform it into its alkali salt, and then to use sodium carbonate for neutralizing the hydrochloric acid formed during the coupling. When coupling with an amine dissolved in hydrochloric acid, sodium acetate is sometimes added during the reaction in order to react with the mineral acid and liberate the feebler acetic acid.

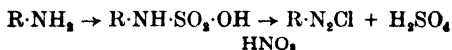
As already stated, the azo-group enters the para-position relative to the hydroxyl, amino, or substituted amino group; if, however, the para-position is already occupied, the entrant group takes up the ortho-position. If neither ortho- nor para-position is free, coupling does not occur, unless the azo-group is capable of displacing the para substituent. With dihydroxy or diamino derivatives of benzene coupling takes place readily when the two groups are in meta-position, thus resorcinol, *m*-phenylenediamine, and *m*-toluylenediamine readily couple with diazonium salts. In the case of resorcinol the azo-groups can be introduced in stages; the first  $\text{N}_2\text{Ph}$  group takes up position 4, the second position 6, and the third position 2.

As the number of azo-groups is increased the shade of the dyestuff is deepened, and at the same time coupling becomes more difficult.

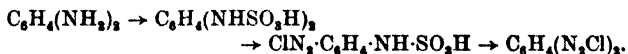
The azo-dyes derived from naphthalene are of greater commercial value than those obtained from benzene. In the case of  $\alpha$ -naphthalene derivatives the azo-group takes up para-(4) position, but if this is not free an ortho (2) azo compound is formed. If position 4 is free, but substituents, especially sulphonic acid groups, are present in positions 3 and 5 then the azo-group enters position 2. With a  $\beta$ -naphthalene derivative, e.g.  $\beta$ -naphthol or  $\beta$ -naphthylamine, the azo-group enters position 1. Coupling with 1 : 2 or 2 : 1-amino-naphthols cannot take place.

As a rule azo-dyes are formed in solution, and are salted out, filtered, dried and ground. Insoluble dyes are frequently prepared on the fabric; an example of such is **para-red**,  $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}_2\cdot\text{C}_{10}\text{H}_6\cdot\text{OH}$ , obtained by steeping cotton in sodium  $\beta$ -naphthoxide solution, squeezing out, drying, and final treatment with a 1 per cent solution of *p*-nitrobenzene-diazonium chloride. Numerous dyes of the same type are obtained by replacing the *p*-nitrobenzenediazonium chloride by the diazonium salts derived from *m*- or *o*-nitraniline,  $\alpha$ -naphthylamine, benzidine, dianisidine, *o*-anisidine, &c. For stabilized diazonium salts cf. p. 1030.

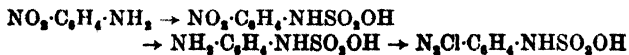
Insoluble or sparingly soluble amines can be converted into readily soluble sulphamic acids by reaction with chlorosulphonic acid and pyridine, and the products can be diazotized with elimination of the N-sulphonic group



with a diamine the disulphamic acids can be diazotized in two distinct stages giving first a diazoaryl-sulphamic acid and finally a tetrazonium salt.



The diazoaryl-sulphamic acids readily couple with  $\beta$ -naphthol yielding soluble dyes. With a nitroamine it is possible to obtain a diazonium salt with the diazo group in place of the nitro group by the following series of reactions, the  $\text{NH}_2$  being converted into the sulphamic acid, the nitro group then





carefully reduced and the product treated with one equivalent of nitrous acid.

When a diazonium salt is readily hydrolysed and cannot therefore be prepared in aqueous solution it is possible to diazotize with nitro-sulphonic acid (chamber crystals or nitrosyl sulphate) in concentrated sulphuric acid. In this way picramide, *s*-tri-nitraniline, can be diazotized. Amines in benzene solution can be diazotized by means of nitrogen peroxide, and it is claimed that this reaction is in harmony with the formula  $O:N\cdot O\cdot NO_2$  for the peroxide (J. A. C. S., 1925, 3011).

The following are some simple monoazo dyes derived from naphthalene. The first name is that of the amine, which is diazotized, and the second is that of the phenol, with which it is coupled:

<b>Ponceau 2G</b>	= Aniline $\rightarrow$ * $\beta$ -naphtholdisulphonic acid R.
<b>Orange G</b>	= Aniline $\rightarrow$ $\beta$ -naphtholdisulphonic acid G.
<b>Orange GT</b>	= Toluidine $\rightarrow$ $\beta$ -naphthol-6-sulphonic acid S.
<b>Palatine Scarlet</b>	= <i>m</i> -Xylidine $\rightarrow$ $\alpha$ -naphthol-3:6-disulphonic acid.
<b>Brilliant Orange R</b>	= Xylidine $\rightarrow$ $\beta$ -naphtholsulphonic acid S.
<b>Ponceau 2R</b>	= <i>m</i> -Xylidine $\rightarrow$ $\beta$ -naphtholdisulphonic acid R.
<b>Palatine Red</b>	= $\alpha$ -Naphthylamine $\rightarrow$ $\alpha$ -naphthol-3:6-disulphonic acid.
<b>Fast Red BT</b>	= $\alpha$ -Naphthylamine $\rightarrow$ $\beta$ -naphtholsulphonic acid S.
<b>Orange II</b>	= Sulphanilic acid $\rightarrow$ $\beta$ -naphthol.
<b>Fast Red</b>	= Naphthionic acid $\rightarrow$ $\beta$ -naphtholsulphonic acid S.
<b>Double Brilliant Scarlet</b>	= Bronner's acid $\rightarrow$ $\beta$ -naphthol.
<b>Sorbine Red</b>	= <i>p</i> -Amino acetanilide $\rightarrow$ $\alpha$ -naphthol-3:6-disulphonic acid.

A number of others are largely used with chrome mordants. Most of these contain as second component salicylic acid, chromotropic acid (1:8-dihydroxynaphthalene-3:6-disulphonic acid) or  $\alpha$ -naphtholsulphonic acid NW, and as 1st component substituted anilines and naphthylamines. For list see *Thorpe and Linstead*, p. 107.

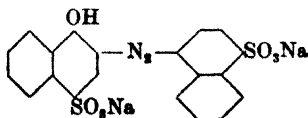
There is a marked difference in the reaction of dyes derived from naphthalene. Those formed with  $\beta$ -naphthol or  $\beta$ -naphthylamine as secondary component are non-reactive, are fast to acids and alkalis, and are of value as finished dyes, whereas

\*  $\rightarrow$  means diazotized and coupled with.

the  $\text{NH}_2$  group in those with  $\alpha$ -naphthylamine as secondary component can be further diazotized and used as intermediates for *dis*- and *tris*-azo-dyes.

**Mordant Colours.**--Although the simple azo-dyes will not dye cotton in the absence of a mordant they can be used for silk and wool.\* The common mordant for a basic dye is tannic acid. The phenolic dyes are used in much the same manner as alizarin, viz. with a metallic mordant (p. 585). The fastest are those on metallic mordants, and the modern method of producing black or blue-black shades for wool dyes is by the action of the mordant rather than by building up poly-azo compounds. The mordant may be applied before dyeing, during the process of dyeing (metachrom process), or the dyed fabric may be treated with a metallic salt. The chrome dyes are usually made with the aid of dichromate and a reducing agent. The following are the common components used in chrome dyes: (1) Base: *o*-amino-phenol, *o*-aminonaphthol, and their sulphonic and carboxylic acids, picramic acid. (2) Second component: all phenols giving *o*-hydroxy-azo compounds, e.g. *p*-naphthol, resorcinol, salicylic acid, and cresotinic acid, phenyl-methyl-pyrazolone,  $\beta$ -diketones,  $\beta$ -ketocarboxylic esters, *m*-phenylenediamine.

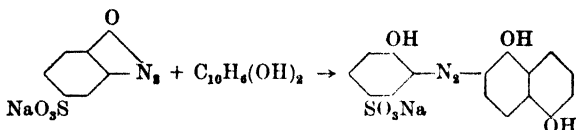
For a simple azo-dye to form a chrome lake it must have one of the following groupings: (i) OH *ortho* to a second OH, or to a carboxylic or similar group. (ii) Same groups as in (i) but in *peri*-positions. (iii) OH *ortho* to an azo-group. (iv) Similar to above but with  $\text{NH}_2$  in place of OH. The first chrome dye was **diamond black F**, and is still one of the commonest,  $\text{CO}_2\text{H}\cdot\text{C}_6\text{H}_3(\text{OH})\cdot\text{N}_2\cdot\text{C}_{10}\text{H}_6\cdot\text{N}_2\cdot\text{C}_{10}\text{H}_5(\text{OH})\text{SO}_3\text{H}$ , from diazotized *p*- (or preferably *o*-) aminosalicylic acid and  $\alpha$ -naphthylamine, the resulting monoazo dye diazotized and coupled with 1-naphthol-4-sulphonic acid (NW acid), also **carmoisine** from naphthionic acid (1-amino-naphthalene-4-sulphonic) and the above NW acid, it dyes



wool red but with a mordant violet.

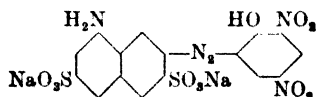
\* For relation between wool-dyeing properties and structure of azo-dyes cf. *Speakman and Clegg*, J. S. D. C. 1934, 348.

**Diamond black PV** is the fastest and best black, and is formed by coupling the *o*-diaz-oxide of 2-aminophenol-4-sulphonic acid with 1 : 5-dihydroxy-naphthalene:

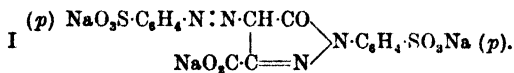


All the chrome lakes are presumably co-ordination compounds (cf. Chap. XLVI, B.). The Cr is attached by covalent links to the phenolic oxygen and by co-ordinate links to a neighbouring oxygen or azo-nitrogen atom forming a chelate ring.

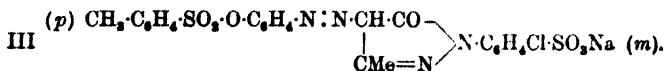
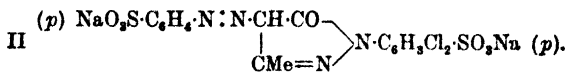
Copper lakes are also known, and many of these are soluble, e.g. picramic acid diazotized and coupled with H acid gives a black dye with a copper mordant:



The most important group of yellow acid dyes are those obtained by coupling a diazonium salt with a pyrazolone derivative (Chap. XLII, A.); the first of these was **tartrazine** (I) (1884), obtained by coupling diazotized sulphanilic acid with the pyrazolone obtained from phenylhydrazine-*p*-sulphonic acid and ethyl oxalacetate and hydrolysing:



More important are **Xylene light yellow 2G** (II), and **Polar yellow 5G** (III).



## 2. DISAZO DYESTUFFS

**Group 1.** These are formed by the successive introduction of two azo-groups—either similar or different—into the molecule of a phenol\* or amine. When one of the couplings takes place in acid solution and involves the introduction of the azo-group into the ring containing the amino group, and the other takes place in alkaline solution and involves the introduction of the azo-group into the ring containing hydroxyl groups, then the two couplings are always effected in the order given, as the former proceeds less readily than the latter, and is retarded to a greater extent as the components become more complex.

A good example is **Wool Black 6B**, obtained by the successive action of diazotized sulphanilic acid in acid solution, and of diazotized  $\alpha$ -naphthylamine in alkaline solution on 1:8-aminonaphthol-4-sulphonic acid. Other examples are:

<b>Resorcin Brown</b>	- <i>m</i> -Xylidine $\rightarrow$ resorcinol $\leftarrow$ sulphanilic acid.
<b>Naphthol Blue-black</b>	- <i>p</i> -Nitraniline $\rightarrow$ aminonaphtholdisulphonic acid H $\leftarrow$ aniline.
<b>Anthracene Acid Brown</b>	- Sulphanilic acid $\rightarrow$ salicylic acid $\leftarrow$ <i>p</i> -nitraniline.
<b>Chrome Patent Green</b>	- Aniline $\rightarrow$ 1-amino-8-naphthol-4:6-disulphonic acid $\leftarrow$ <i>p</i> -nitraniline.
<b>Palatine Black</b>	- Sulphanilic acid (acid solution) $\rightarrow$ 1-amino-8-naphtholdisulphonic acid H $\leftarrow$ $\alpha$ -naphthylamine.

The amine mentioned first is diazotized, then coupled with the middle compound, and finally the last-mentioned substance is diazotized and coupled with the monoazo dye formed from the first two.

**Group 2.** The members of this group are synthesized by first preparing an amino-azo compound, diazotizing the amino group in this, and coupling the product with an amine or phenol.

A complex member is **naphthol black B**,  $(\text{SO}_3\text{Na})_2\text{C}_{10}\text{H}_5\cdot\text{N}:\text{N}\cdot\text{C}_{10}\text{H}_5\cdot\text{N}:\text{N}\cdot\text{C}_{10}\text{H}_4(\text{OH})(\text{SO}_3\text{Na})_2$ , and is formed by diazotizing  $\beta$ -naphthylamine-6:8-disulphonic acid, coupling with  $\alpha$ -naphthylamine, then diazotizing the resulting amino-

\* For influence of various groups in the phenol molecule on coupling compare *Auwers and Michaelis, B.*, 1914, 1275.

azo compound and coupling with an alkaline solution of  $\beta$ -naphthol-3 : 6-disulphonic acid. Other examples are:

<b>Biebrich Scarlet</b>	= Aminoazobenzenesulphonic acid (from acid yellow) $\rightarrow$ $\beta$ -naphthol.
<b>Sudan III</b>	= Aminoazobenzene $\rightarrow$ $\beta$ -naphthol.
<b>Brilliant Crocein</b>	= Aminoazobenzene $\rightarrow$ $\beta$ -naphtholdisulphonic acid G.
<b>Diamond Green</b>	= Aminosalicylic acid-azo- $\alpha$ -naphthylamine $\rightarrow$ dihydroxynaphthalenesulphonic acid S.
<b>Crocein Scarlet 8B</b>	= Aminoazotoluenesulphonic acid $\rightarrow$ $\beta$ -naphthol-8-sulphonic acid.
<b>Ponceau 4RB</b>	= Aminoazobenzenesulphonic acid $\rightarrow$ $\beta$ -naphthol-8-sulphonic acid.
<b>Cromassie Navy Blue 2RNX</b>	= Metanilic acid-azo- $\alpha$ -naphthylamine $\rightarrow$ tolyl- $\alpha$ -naphthylamine-8-sulphonic acid.
<b>Nerol B</b>	= <i>p</i> -Aminodiphenylamine- <i>o</i> -sulphonic acid azo- $\alpha$ -naphthylamine $\rightarrow$ $\beta$ -naphtholdisulphonic acid R.

As great difficulty is experienced in diazotizing naphthalene derivatives in which the amino and azo groups are ortho to one another, it is necessary to use *p*-aminoazo compounds, and hence derivatives of  $\alpha$ -naphthylamine are commonly used.

**Group 3. Direct Cotton Dyes or Substantive Dyes.** This important group comprises the disazo dyestuffs obtained by diazotizing a primary diamine and coupling the tetrazonium salt with two molecules of an amine or phenol. The compounds of commercial importance are those derived from benzidine (*pp'*-diaminodiphenyl, Chap. XXVII) and its homologues, the tolidines. When two molecules of the same amine or phenol are used, the products are *simple* benzidine dyestuffs, e.g. **Congo-red** from tetrazobenzidine chloride and sodium naphthionate,  $\text{SO}_3\text{Na} \cdot \text{C}_{10}\text{H}_5(\text{NH}_2)\text{N}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C}_6\text{H}_4 \cdot \text{N}_2 \cdot \text{C}_{10}\text{H}_5(\text{NH}_2)\text{SO}_3\text{Na}$ .

Intermediate compounds of the type  $\text{ClN}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C}_6\text{H}_4 \cdot \text{N}_2 \cdot \text{C}_{10}\text{H}_5(\text{NH}_2) \cdot \text{SO}_3\text{Na}$  can be prepared as crystalline salts, but are of no technical importance. The coupling with the second molecule of amine proceeds slowly, and may, in certain cases, take several days for completion.

The benzidine dyes are of great commercial value, as they are **substantive dyes**; that is, they can dye cotton fabrics without the aid of a mordant. All benzidines which contain substituents in the ortho-positions with respect to the amino groups can yield substantive dyes, whereas the disazo compounds derived from benzidine derivatives with meta substituents, e.g. *pp'*-diamino-*o-o'*-dicarboxylic acid or the corre-

sponding halogen derivatives or sulphonic acids, exhibit no affinity for the vegetable fibre.

Numerous other *p*-diamines can also yield substantive dyes, e.g. *pp*-diaminostilbene (Chap. XXIX),  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$ ; *pp*-diaminodiphenylamine,  $\text{NH}(\text{C}_6\text{H}_4\cdot\text{NH}_2)_2$ ; *pp*-diaminodiphenylcarbamide,  $\text{CO}(\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2)_2$ ; *pp*-diaminocarbazole; *pp*-diaminofluorene and *pp*-diamino-azobenzene,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}_2\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$ . *p*-Phenylenediamine and 1:4- and 1:5-diaminonaphthalenes also yield substantive dyes, whereas *pp*-diaminodiphenylmethane (Chap. XXVIII) and *pp*-diaminodibenzyl,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$ , do not.

The number of combinations between such diamines and various phenols, amines, and their sulphonic acids is extremely large, and only a few of the resulting substantive dyes can be mentioned:

<b>Chrysamine G</b>	- Benzidine $\rightarrow$ salicylic acid (2 mols.).
<b>Diamine Black BH</b>	- Benzidine $\rightarrow$ $\gamma$ -aminonaphtholsulphonic acid and aminonaphtholdisulphonic acid H.
<b>Chrysophenine G</b>	- Diaminostilbenedisulphonic acid $\rightarrow$ phenetole (2 mols.).
<b>Cotton Yellow G</b>	- Diaminodiphenylurea $\rightarrow$ salicylic acid (2 mols.).
<b>Diamine Blue BX</b>	{ - Benzidine $\rightarrow$ $\alpha$ -naphtholsulphonic acid NW. $\gamma$ -aminonaphtholdisulphonic acid H.
<b>Benzopurpurine 4B</b>	
<b>Diamine Blue BX or Niagara Blue BX</b>	{ - Tolidine $\rightarrow$ naphthionic acid (2 mols.). $\alpha$ -naphtholsulphonic acid NW. aminonaphtholdisulphonic acid H.
<b>Diamine Sky Blue</b>	
<b>Acid Anthracene Red 3B</b>	- Dianisidine $\rightarrow$ 1:8-aminonaphthol-2:4-disulphonic acid (2 mols.).
<b>Carbazol Yellow</b>	- <i>o</i> -Tolidinedisulphonic acid $\rightarrow$ $\beta$ -naphthol (2 mols.).
<b>Milling Scarlet</b>	- Diaminocarbazol $\rightarrow$ salicylic acid (2 mols.). - 4:4'-Diamino-2:2'-dimethyl-diphenylmethane $\rightarrow$ $\alpha$ -naphthol-5-sulphonic acid L (2 mols.).
<b>Diamine Black BH</b>	{ - Benzidine $\rightarrow$ aminonaphthol- $\gamma$ -sulphonic acid. aminonaphtholdisulphonic acid (both in alkali).
<b>Chlorazol Sky Blue FF</b>	
<b>Cotton Yellow G</b>	- Dianisidine $\rightarrow$ 1:8-aminonaphthol-2:4-disulphonic acid (2 mols. in alkali).
<b>St. Denis Red</b>	- Di- <i>p</i> -aminodiphenylurea $\rightarrow$ salicylic acid (2 mols.). - Diaminoazoxytoluene $\rightarrow$ $\alpha$ -naphtholsulphonic acid NW.

The following rules apply to diamines which yield substantive cotton dyes: (1) If the amino groups are in different nuclei they must be *para* to the union of the two nuclei or to the chain joining the nuclei. (2) The chain must be unsaturated (C:C) or contain an atom with pairs of lone electrons, e.g. —NH— or —N—N—. (3) With derivatives of diphenyl



the position *ortho* to the union must be unsubstituted or form part of a ring. (4) If the amino groups are in the same ring they must be *para* or, in the case of naphthalene, 1:5 or *para* to one another. Unless these conditions are fulfilled the amine will yield disazo compounds which cannot dye cotton direct.

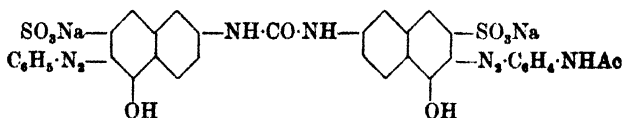
Another group of direct cotton dyes are those derived from J acid, 2-amino-5-naphthol-7-sulphonic acid and its derivatives. They are much faster than benzidine dyes, particularly to acids. Examples are:

**Brilliant Benzoviolet 2RL**, by diazotizing H acid and coupling with *m*-toluidine and then diazotizing and coupling with phenyl J acid (i.e. Ph in NH<sub>2</sub>).

**Brilliant Fast Blue** from H acid,  $\alpha$ -naphthylamine and phenyl J acid.

**Rosanthere O** from diazotized aniline and *m*-aminobenzoyl J acid, i.e.  $\cdot\text{CO}\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$  (*m*) in NH<sub>2</sub> of J acid, and can be made faster by diazotizing and developing with  $\beta$ -naphthol.

**Benzo Fast Scarlet 4BS**. Two molecules of J acid are condensed with phosgene and sodium carbonate, and the intermediate coupled first with diazotized aniline and then with diazotized *p*-aminoacetanilide. Its structure is



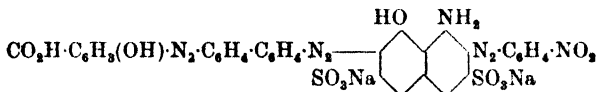
**Bismarck brown**,  $\text{C}_6\text{H}_4[\text{N}_2\cdot\text{C}_6\text{H}_3(\text{NH}_2)_2]_2$  (Chap. XXII E.), is a bisazo dye derived from a metadiamine, and can only be used on cotton in the presence of a tannin mordant, but dyes wool a red-brown shade.

## 3. TRISAZO DYESTUFFS

These contain three azo-groups. One method of preparing such compounds is by starting with a bisazo dyestuff, e.g. a benzidine dye, containing an amino group, diazotizing this and coupling the product with an amine or a phenol. Thus the dye produced by coupling diazotized benzidine with  $\alpha$ -naphthylamine and 7-amino- $\alpha$ -naphthol-3:6-disulphonic acid can be further diazotized and the product coupled with amino-naphthol-sulphonic acid Y, when the dye **Direct Black V** is obtained.

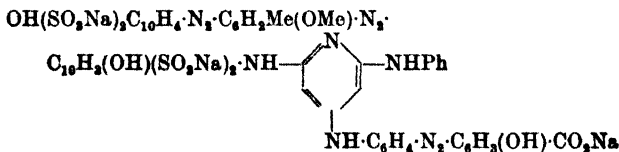
A second method is to couple a diazonium salt with one of the components present in a benzidine dye; thus **Congo-brown G** is formed by allowing diazotized sulphanilic acid to couple with the resorcinol residue in the bisazo dye derived from benzidine, salicylic acid, and resorcinol.

**Diamine green B**, a green substantive dyestuff, is manufactured by coupling diazotized *p*-nitraniline with 8-hydroxy-1-naphthylamine-3:6-disulphonic acid (H acid), then coupling benzidine tetrazonium salt with this and finally with salicylic acid. Its structural formula is



With phenol in place of salicylic acid diamine green B is formed.

An important fast green azo-dye is **Chlorantine Fast Green BLL** (1924) which contains the cyanuric ring (Chap. XII, C.):



Various other fast dyes with the same ring are of value.

## 4. TETRAKISAZO DYESTUFFS

These can be prepared by the action of two molecules of a diazonium salt on a suitable bisazo dyestuff; thus the dye derived from benzidine and resorcinol (2 mols.) couples with diazotized salicylic acid, yielding **Hessian brown BB**.



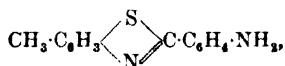
Another method of formation is the coupling of two molecules of the intermediate tetrazo compound, formed in the production of a benzidine dye, with one molecule of dihydroxy-diphenyl-methane or with a similar compound.

Most of the dyestuffs are brown, and have only a limited importance.

In the benzidine dyes, as in many other series of azo-dyes, the presence of chlorine atoms renders the products much faster to light. *m-m*-Dichlorobenzidine gives rise to the products known as **dianol reds**, and **chlorazol blues** are obtained by coupling the tetrazo derivative of dianisidine with chlorinated naphtholsulphonic acids.

Many of the direct cotton dyes are also used on wool. On cotton some exhibit sensitiveness to washing and acids, but can be rendered much faster by an "after-treatment" with either a weak chrome bath, formaldehyde or sodium thiosulphate.

A few monoazo direct cotton dyes are known; these are mostly derived from dehydrothio-*p*-toluidine,



and its homologues or from primuline-sulphonic acid by diazotizing and coupling with salicylic acid or naphtholsulphonic acid.

## 5. INGRAIN COLOURS

Some of the more complex azo dyestuffs are actually prepared on the fabric, and are termed Ingrain colours. This may be accomplished in one of two ways:

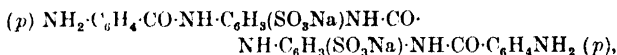
(a) *Coupling on the fibre*.—In order to obtain complex dyes, the fabric which has been dyed with a substantive dye is sometimes treated with a solution of *p*-nitrobenzenediazonium chloride. For this purpose the substantive dye must contain a residue capable of coupling with a diazonium salt.

To facilitate the production of ingrain dyes diazo compounds are now supplied in the dry form. (1) The diazonium salt with warm aqueous sodium hydroxide yields the sparingly soluble sodium salt  $\text{R}\cdot\text{N}:\text{N}\cdot\text{ONa}$ , which is stable and can be sent out as a paste—"nitrosamine red paste"; for coupling purposes it must be acidified. (2) Many diazonium compounds

form stable complex salts, e.g. hydrofluor-titanates, -stannates or -aluminates, and are sent out in solid form.

(b) *Developing on the fibre*.—When the fabric has been dyed with a dyestuff containing an amino group, it is subsequently treated with nitrous acid and then with a bath of  $\beta$ -naphthol, when a more complex dye is actually produced on the fibre. Thus to produce **Diazo black B** the fabric is dyed with the substantive dye derived from benzidine and 1-naphthylamine-5-sulphonic acid, which is then diazotized on the fabric and developed with  $\beta$ -naphthol for blue-black or with *p*-phenylenediamine for brown-black shades.

The complex fast yellow dye, **Diazo light yellow 2G** (1910), is made by impregnating the cloth with



then diazotizing and developing with 1-phenyl-3-methyl-5-pyrazolone.

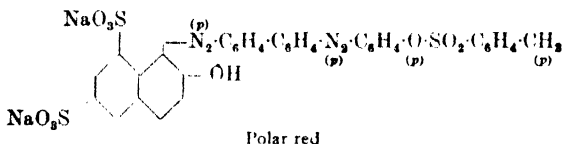
As the temperature necessary for coupling or developing is low they are often termed **ice colours**.

The reverse process is frequently used, viz. the fabric is padded with an alkaline solution of  $\beta$ -naphthol and finally developed by immersion in a bath of a diazotized base (cf. *Thorpe and Linstead*, p. 125).

A great improvement has been effected by using naphthol AS, i.e. the anilide of 2-hydroxy-naphthalene-3-carboxylic acid,  $\text{OH} \cdot \text{C}_{10}\text{H}_6 \cdot \text{CO} \cdot \text{NHPh}$ , or any similar arylide. The intermediates are substantive to cotton, and the dyes are more brilliant in colour and faster than those obtained from  $\beta$ -naphthol itself (*Rowe and others*, J. Soc. Dyers, 1921, 204; 1924, 218; 1930, 227). Numerous red, orange and purple dyes are formed, and also pure navy blue shades, e.g. by developing naphthol AS or similar compounds on the fibre with diazotized 4-amino-4'-ethoxy-diphenylamine,  $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{OEt}$  (Variamine Blue B base).

**Hansa yellows**, used as solid yellow pigments, are formed by coupling diazotized monamines with arylides of acetoacetic acid. **Hansa yellow G** is  $\text{NO}_2 \cdot \text{C}_6\text{H}_2\text{Me} \cdot \text{N}_2 \cdot \text{CH}(\text{COCH}_3) \cdot \text{CO} \cdot \text{NHPh}$ . When pyrazolones are used in place of the arylide the pigments have redder shades, e.g. **Permanent yellow R** (1911) is the product from diazotized *o*-chloraniline and 1-*p*-nitrophenyl-3-methyl-5-pyrazolone.

Numerous attempts have been made to improve the fastness of azo dyestuffs to milling, washing, &c. As already pointed out (Chap. XXIV), aromatic compounds with  $\text{NH}_2$  and  $\text{OH}$  groups are extremely reactive, and the methods adopted to improve the fastness is to protect either  $\text{OH}$  or  $\text{NH}_2$  groups. To protect  $\text{OH}$  groups three methods are available: (i) Treatment with formaldehyde, giving the **vulcan** dyes. (ii) Alkylation, e.g. introduction of  $\text{Et}$ ,  $\text{-CH}_2\text{Ph}$  or higher alkyl groups; thus the benzyl ether of 4-chloro-2-amino-phenol is an extremely good intermediate. (iii) By condensation of the dye with *p*-toluene-sulphonyl chloride when the  $\text{OH}$  yield  $\text{O}\cdot\text{O}_2\text{S}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$ , giving the important **polar colours**, e.g.:



An  $\text{NH}_2$  group is usually protected by somewhat similar methods: (1) by alkylation groups as complex as decyl can be introduced, (2) by introducing the  $\cdot\text{SO}_2\text{NH}_2$  or  $\cdot\text{CO}\cdot\text{NH}_2$ .

**Viscose-rayon Dyestuffs.**—Many of the azo-dyes used for cotton can also be used for viscose-rayon, but often do not give level colours, and hence a special group of dyes is used for viscose. The most important are the **Icyl** dyes, which are of two types: (1) Diazo dye of the type  $\text{A} \rightarrow \text{B} \rightarrow \text{C}$ , where A is a nitrated amine or derivative and C is an aminonaphthol sulphonic acid, S acid, J acid, or H acid. (2) Dyes derived from symmetrical diamines, e.g. 2:2'-substituted benzidines or 4:4'-diamino-diphenylsulphide, 4:4'-diamino-diphenylamine and the secondary components J acid, or 1:8- and 2:8-amino-naphthol sulphonic acid.

## C. Stilbene, Pyrazolone, and Thiazole Dyestuffs

### 1. STILBENE DYESTUFFS

This group comprises a number of yellow and orange substantive dyestuffs which are relatively fast. The elucidation of the constitution is due to A. G. Green (J. C. S., 1904, 1424, 1432; 1906, 1602; 1907, 2076; 1908, 1721), who obtained

from them diaminostilbenedisulphonic acids by reduction and benzaldehydesulphonic acids by oxidation with permanganate. By the action of hot caustic soda on *p*-nitroluene-*o*-sulphonic acid, **sun yellow** or **direct yellow RT** (*Walther*, 1883) is formed, and this with hypochlorite gives **Mikado yellow**, and reduced gives **Mikado orange**.

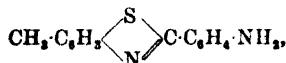
The first product formed in the condensation of *p*-nitro-toluene-*o*-sulphonic acid with alkali is a *p*-nitroso-*p'*-nitro-di-benzylsulphonic acid together with water. Under the influence of reducing substances present this forms *pp'*-dinitrostilbenedisulphonic acid, which undergoes further reduction to direct yellow RT, which is an azo-azoxy derivative of stilbene,



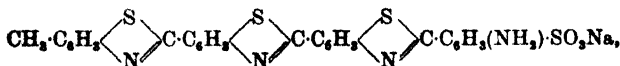
**Mikado yellow** is the corresponding dinitroazostilbenedisulphonic acid, which can also be formed by reducing 4 : 4'-dinitrostilbene-3 : 3'-disulphonic acid. **Stilbene orange 4R** is the corresponding compound containing two azo groups in place of one azo and one azoxy group, and is formed when the condensation takes place in the presence of glycerol.

## 2. THIAZOLE DYESTUFFS

The **primulines** (*Green*, 1887) are thiazole derivatives (Chap. XLII, B.). Primuline base itself is formed together with dehydrothiitoluidine, *p*-aminobenzothiazole,

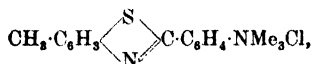


by heating *p*-toluidine with sulphur at about 200°, and is generally used in the form of a sulphonic acid with SO<sub>3</sub>Na ortho to the CH<sub>3</sub> group. **Primuline yellow** is probably a mixture of a di- and trithiazole derivative, e.g.:



and is not fast. **Thioflavine S** is a methyl derivative of primuline, and gives canary yellow colours to tanned cotton. **Thio-**

**flavine T**, obtained from dehydrothiitoluidine, methyl alcohol, and HCl at 170° is the ammonium chloride,



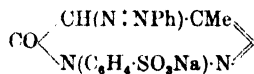
and gives greenish-yellow shades. The primulines themselves are of little use as direct dyes, but the fabric treated with a primuline can be diazotized and developed with hydroxy- or amino-compounds yielding very fast yellow to brown ingrain colours.

### 3. PYRAZOLONE DYESTUFFS

These are mainly azo dyestuffs containing the pyrazolone ring (Chap. XLII, A.). They are yellow dyes, fast to light but relatively expensive, e.g. **tartrazine** (Ziegler, 1884).

They have been referred to already under fast and yellow dyes (section B4).

Numerous dyes can be prepared by coupling simple diazonium salts with pyrazolonesulphonic acids. **Fast light yellow G**, obtained from benzenediazonium chloride and 1-*p*-sulphophenyl-3-methyl-5-pyrazolone, is



or the corresponding enol.

**Eichrome red B** is obtained from 1-amino-2-naphthol-4-sulphonic acid and 1-phenyl-3-methyl-5-pyrazolone.

## D. Di- and Triphenylmethane Dyes

The basic and acidic dyes derived from triphenylmethane have been dealt with in Chap. XXX.

The only important dyestuff of the diphenylmethane series is **Auramine O**, the ketoneimide,  $\text{NMe}_2\cdot\text{C}_6\text{H}_4\cdot\text{C}(\text{:NH})\cdot\text{C}_6\text{H}_4\cdot\text{NMe}_2$ , HCl, or  $\text{NMe}_2\cdot\text{C}_6\text{H}_4\cdot\text{C}(\text{NH}_2)\cdot\text{C}_6\text{H}_4\cdot\text{NMe}_2\text{Cl}$ . This was originally prepared (Kern and Caro, 1883) by heating *Michler's* ketone, tetramethyl-4:4'-diaminobenzophenone, with ammonium and zinc chlorides at 160°, but is now generally manufactured by fusing tetramethyldiamino-diphenylmethane with

sulphur, ammonium chloride, and common salt, whilst ammonia is passed through the mass;  $\text{H}_2\text{S}$  is formed, and the  $\text{CH}_3$  group gives rise to the  $\text{C:NH}$  group. **Auramine G** is the corresponding compound derived from *o*-toluidine.

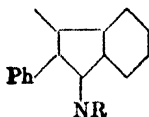
The following dyes are derivatives of diphenylnaphthylmethane,  $\text{CHPh}_2\cdot\text{C}_{10}\text{H}_7$ . **Victoria blue B**, obtained by condensing phenyl- $\alpha$ -naphthylamine (p. 576) with tetramethyl-4:4'-diaminobenzhydrol or tetramethyl-4:4'-diaminobenzophenone chloride, is  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{C}_{10}\text{H}_6\cdot\text{C}(\text{C}_6\text{H}_4\cdot\text{NMe}_2):\text{C}_6\text{H}_4\cdot\text{NMe}_2\text{Cl}$ . **Victoria blue R** is obtained in a similar manner from ethyl- $\alpha$ -naphthylamine, and **night blue** from tetraethyl-diaminobenzophenone chloride and *p*-tolyl- $\alpha$ -naphthylamine. These blues are not very fast to light, but give very bright shades. **Wool green** is formed by condensing G salt (p. 574) with tetramethyldiamino-benzophenone chloride.

*Influence of constitution on colour in the Triphenylmethane Group* (cf. Chap. XXX).—The introduction of six methyl groups into the  $\text{NH}_2$  groups of magenta gives crystal violet, and with fewer the intermediate violets are formed. The introduction of methyl groups into the nuclei, e.g. one methyl in each ring as in new magenta still gives a red colour. The gradual introduction of phenyl groups in the  $\text{NH}_2$  causes a change of colour from red to blue. The removal of one amino group, e.g. malachite green, produces a marked effect, and similar effects are obtained by acylating the amino groups.

The position of the  $\text{NH}_2$  groups is important, e.g. fast green has three  $\text{NH}_2$  groups, two in *para*- and the third in *meta*-position, so that a meta  $\text{NH}_2$  group has no effect.

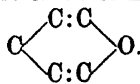
If two  $\text{NH}_2$  groups are removed the colour changes to yellow, giving a dyestuff which can be used with tannined cotton. The replacement of  $\text{NH}_2$  by  $\text{OH}$  gives the aurines which are yellow.

The fastness of a compound of the malachite green groups is greatly enhanced by replacing one or more phenyl groups by indoyl nuclei, especially the group



## E. Xanthene Dyestuffs

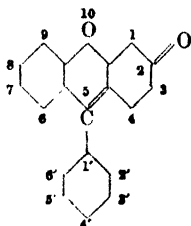
These dyestuffs, which can be regarded as derivatives of diphenylmethane oxide or xanthene (Chap. XLIV, B.), contain

the pyrone ring . They are usually divided into the two groups:

1. The **pyronines**, or derivatives of diphenylmethane, and
2. The **phthaleines**, or derivatives of triphenylmethane.

The formation and structure of the phthaleines have been dealt with in Chap. XXX. The chief members of this class are the eosines, the rhodamines, and galleine.

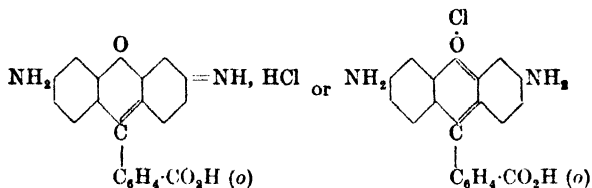
The following numbering of the atoms in the fluorescein skeleton is adopted:



This numbering is not the same as that given in *Richter's* Lexicon, but is analogous to that adopted for acridine, phenazine, &c.

**Uranine** or sodium fluorescein is the sodium derivative of the 8-hydroxy-2'-carboxylic acid. **Eosin A** is 1 : 3 : 7 : 9-tetrabromofluorescein. **Spirit eosin** and **Eosin S** are the corresponding methyl and ethyl esters. **Eosin BN** is potassium 3 : 7-dinitro-1 : 9-dibromofluorescein. **Erythrosin G** is potassium 1 : 9-diiodofluorescein, **Erythrosin** is 1 : 3 : 7 : 9-tetraiodofluorescein. **Phloxine P** is potassium 4' : 5'-dichloro-1 : 3 : 7 : 9-tetrabromofluorescein. **Rose Bengal** is the corresponding tetraiodo compound. **Phloxine** is potassium 3' : 4' : 5' : 6'-tetrachloro-1 : 3 : 7 : 9-tetrabromofluorescein. **Gallein** or **alizarin violet**, from gallic acid and phthalic anhydride, is 1 : 9-dihydroxyfluorescein. **Coerulein** is gallein anhydride formed by the elimination of water from the OH of the carboxyl group and hydrogen in position 4.

The **Rhodamines** or aminophthaleins contain  $\text{NH}_2$  and  $\text{NH}$  or substituted  $\text{NH}_2$  and  $\text{NH}$  groups in place of the  $\cdot\text{OH}$  and  $\text{:O}$  groups of fluorescein. The bases themselves probably have a lactam structure, but the salts (dyes) may be represented by para or ortho quinonoid formulæ, probably the latter, with a quadrivalent oxygen atom, as fluorescein and derivatives, which contain no  $\text{NH}_2$  groups, also from chlorides which can dye tanned cotton.



The numbering is the same as in the fluorescein skeleton.

The rhodamines are manufactured by condensing phthalic anhydride with substituted aminophenols. The presence of a carboxylic group in the salts, and hence a quinonoid structure, is indicated by the readiness with which the dyes yield alkyl derivatives, which are readily hydrolysable, i.e. esters; these are also coloured. If the dyes were lactones the products formed on alkylation would be quaternary ammonium salts, which should not be readily hydrolysed.

**Rhodamine B** contains two  $\text{NEt}_2$  groups in positions 2 and 8. **Rhodamine 3B** is the corresponding ethyl ester. **Rhodamine 6G** is the ester containing two  $\text{NHet}$  groups in 2 and 8 positions. **Rhodamine S** is the chloride of the dimethyl-amino compound containing the group  $\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  (derived from succinic acid) attached to C No. 5. **Viola-mines** contain phenyl and tolyl, and sulphonated phenyl groups attached to the N atoms in positions 2 and 8.

**Rhodamine 5G** (1902) contains Me in positions 3 and 7,  $\text{NHMe}$  in positions 2 and 8, and a Cl in 2' and is a brilliant red dye. It is fast due to the halogen and is made from *o*-chlorobenzaldehyde and 2-methyl-amino-*p*-cresol by action of  $\text{H}_2\text{SO}_4$  and subsequent oxidation.

New compounds contain the group  $\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot$  in 2 and 8 and are formed by the action of *p*-aminophenols on 2:8 dihalogenated fluoresceins.

Acid dyes with  $\text{SO}_3\text{H}$  groups are known, e.g. **Fast acid violet**



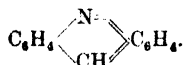
**A<sub>2</sub>R** with  $:\text{NH}\cdot\text{C}_6\text{H}_3\text{MeSO}_3$  in 2,  $\cdot\text{NH}\cdot\text{C}_6\text{H}_4\text{Me}$  in 8, and  $\text{CO}_2\text{Na}$  in 2', is obtained by condensing *m*-hydroxy-di-*o*-tolyl-amine with phthalic anhydride and subsequent sulphonation.

Dyes with an ester structure such as Rhodamine 3B or 6G or Eosin S are as a rule faster and more stable, as the conversion of the  $\cdot\text{COONa}$  group to  $\cdot\text{COOEt}$  lessens the tendency to the formation of colourless lactones. They have a bluer shade and can be used as direct dyes for cotton.

The pyronines are of but little importance, and are formed by condensing alkylated *m*-aminophenols with aliphatic aldehydes or acids, e.g. **pyronine G** from formaldehyde and dimethyl-*m*-aminophenol and subsequent oxidation.

## F. Acridine and Quinoline Dyes

The chromogene in the acridine dyestuffs is the acridine ring (Chap. XLIV, B.) with an orthoquinonoid structure,



They are analogous to the xanthene dyestuffs, and by replacing the H of the CH group by phenyl, triphenylmethane derivatives are obtained. The only compounds of commercial importance are the amino or substituted amino derivatives, with the nitrogen atoms in the positions 2 and 8. They are yellow and orange to brown basic dyes used in calico printing, and also used in dyeing cotton, silk, jute and particularly leather, and some are of value medicinally.

**Acridine yellow**,\* 2 : 8-diamino-3 : 7-dimethylacridine hydrochloride, is a basic yellow dye obtained by condensing *m*-toluylenediamine with formaldehyde and oxidizing the resulting leuco-base. The corresponding 5-phenyl derivative is **benzoflavine**. **Acridine orange**, 2 : 8-tetramethyldiaminoacridine zinc chloride, is obtained from *m*-aminodimethylaniline and formaldehyde and **Acridine orange R extra** is the corresponding 5-phenyl derivative obtained by using benzaldehyde. **Phosphine** or leather yellow is impure chrysaniline, 2 : 4'-dia-

\* The numbering is exactly similar to that of fluorescein derivatives (p. 1036), the N atom occupying the position of the pyrone oxygen in fluorescein.

minophenylacridium nitrate, and is obtained as a by-product in the manufacture of magenta (Chap. XXX, 2).

Common quinoline dyes are mentioned in Chap. XLIV, A2.

**Cyanine dyes.**—The cyanine dyes are of great value as sensitizers for the photographic plate, e.g. in the production of panchromatic plates, i.e. plates which are nearly equally sensitive to all parts of the spectrum: pinacyanol which sensitizes right into the red and pinaverdol which sensitizes through the green into the red, are two of the oldest dyes introduced by *König* (1902), but numerous others have been prepared during 1917 to 1936, and the structure of many has been elucidated by *Mills* and his co-workers both by processes of oxidation and by syntheses.

They all contain two heterocyclic nitrogen-containing rings, the nitrogen in one being in the tervalent state and in the other in the quinquevalent or ammonium salt form. In some of the newer dyes a nitrogen-sulphur ring, e.g. benzthiazole ring, may replace one or both of the rings. As a rule the two rings are quinoline rings, but a few dyes containing pyridine rings are known.

The two rings may be directly united, but usually are joined by the  $\cdot\text{CH}:$  or  $\cdot\text{CH}:\text{CH}:\text{CH}:$  group, or a longer chain containing alternate single and double linkings. The colour of the dyes is attributed to these alternate double linkings being in conjugation with linkings in the rings. The sub-division of the dyes is as follows (cf. *Koenigs*, B., 1922, 3293; *Mills*, J. C. S., 1928, 1918):

I. Nitrogen rings directly united = **Apocyanines**.

II. Nitrogen rings attached by a  $\cdot\text{CH}:$  group:

(a) 2 : 2'-attachment\* = **Pseudocyanines**.

(b) 2 : 4'-attachment = **Isocyanines**.

(c) 4 : 4'-attachment = **Cyanines**.

III. Nitrogen rings united by a  $\text{a}:\text{CH}:\text{CH}:\text{CH}:$  group = Carbo-cyanine dyes:

(a) 2 : 2'-attachment = **Pinacyanols**.

(b) 2 : 4'-attachment = **Dicyanines**.

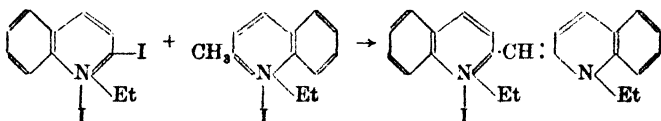
(c) 4 : 4'-attachment = **Kryptocyanines**.

\* The N atoms are numbered 1 and 1'.

## IV. Thiocyanines.

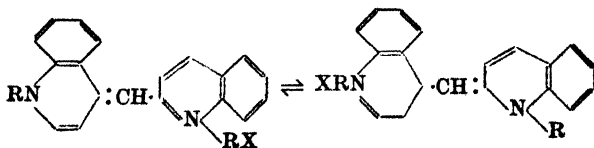
I. **Apocyanines**.—(a) Xanthoapocyanines with 3:2'-attachment and (b) Erythroapocyanines with 3:4'-attachment. A mixture of two such dyes is formed by the action of alcoholic potash on a quinoline ethiodide. The structure of the latter has been established by *Mills and Ordish* (1928, 81) by oxidizing it with iodine to 3:4'-diquinolyl ( $C_9H_8N$ )<sub>2</sub>, which has been directly synthesized.

II. (a) The **pseudocyanines** can be prepared by the action of alcoholic potash on 2-iodoquinoline methiodide and quinaldine methiodide (*Hamer*, 1928, 206), and similar compounds. They exert a sensitizing action in the bluish-green region of the spectrum. The condensation occurs between the iodine atom in position 2 of one nucleus and a hydrogen atom of the methyl group in position 2 of the second nucleus, also elimination of HI from the ammonium iodide and hydrogen of the  $CH_3$ . They are ammonium salts with a quadrivalent N in the cation.



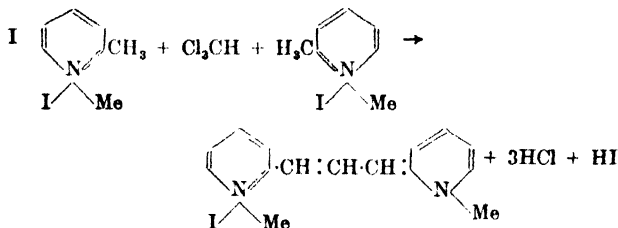
(b) **Isocyanines** can be synthesized by a process similar to the above but using 4-chloroquinoline alkyl iodides. The structure has been confirmed by oxidation, e.g. dimethylisocyanine acetate when oxidized yields 1-methyl-2-quinolone (NMe in position 1 and CO in position 2) and cinchoninic acid methochloride (NMeCl in 1 and  $CO_2H$  in 4) (*Mills and Wishart*, J. C. S., 1920, 579). The most valuable are 1:1'-diethylisocyanine or **Ethyl Red**, and 1:1':6-trimethylisocyanine or **Sensitol**.

Isocyanines and all cyanines which are not symmetrical are tautomeric as indicated by the following scheme:



### III. Carbocyanines.

(a) **2:2'-Carbocyanines.**—One of the simplest of these is 2:2'-carbopyridine cyanine (I) obtained by the action of chloroform and potash on  $\alpha$ -picoline alkyl iodides (B., 1929, 2724).



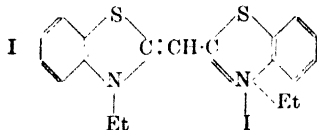
By using  $\gamma$ -picoline the isomeric 4:4'-cyanine is formed. In all the syntheses of carbocyanines the chain,  $\cdot\text{CH}:\text{CH}:\text{CH}\cdot$ , is built up from the two reactive methyl groups present in two substituted pyridine or quinoline rings, and a third carbon atom introduced in the form of chloroform, formaldehyde, ethyl orthoformate or the complex diorthoformylmethylaminodiphenyl disulphide,  $\text{O}:\text{CH}\cdot\text{NMe}\cdot\text{C}_6\text{H}_4\cdot\text{S}\cdot\text{S}\cdot\text{C}_6\text{H}_4\cdot\text{NMe}\cdot\text{CH}:\text{O}$ , in pyridine solution (*Mills and Odams*, J. C. S., 1924, 1914).

One of the first known cyanine dyes, **pinacyanol** (1:1'-diethyl-2:2'-carbocyanine iodide), known also as **sensitol red**, is more active than isocyanines. It is a 2:2'-carbocyanine with quinoline rings, and is formed by the action of potash and formalin on mixtures of ethiodides of quinoline and quinaldine. Its structure follows from the fact that on oxidation it yields 1-ethyl-2-quinolone (NEt in 1, CO in 2) and quinaldinic acid ethyl nitrate (NEtNO<sub>2</sub> in 1 and  $\cdot\text{CO}_2\text{H}$  in 2) (*Mills and Hamer*, 1920, 1550), and hence is a 2:2'-carbocyanine with two quinoline residues and NEt in position 1 and NEtX in position 1'. It has been synthesized from quinaldine ethiodide and ethyl orthoformate in presence of acetic anhydride and zinc chloride.

(c) **Kryptocyanines** can be synthesized in a similar manner, using 4-methylquinoline (lepidine) alkyl iodides (*Mills and Braunholz*, 1923, 2804), and dicyanines by using a mixture of alkyl nitrates of quinaldine and lepidine; in this synthesis small amounts of 2:2'- and 4:4'-carbocyanines are formed,

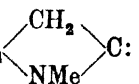
but the chief product is the 2:4'- or dicyanine (*Mills and Odams*, 1924, 1913; *Hamer*, 1927, 2796).

IV. **Thiocyanines**, e.g. diethylthiocyanine, I, can be synthesized by the action of ethyl malonate on *o*-aminothiophenol, converting the product into the mono ethiodide, removing HI by alkali, and then converting the second N into its ethiodide (*Mills*, 1922, 455, 1489).



Thiocarbocyanines (*König*, B., 1928, 2065; *Hamer*, J. C. S., 1928, 3160) and selenocarbocyanines (J. C. S., 1928, 2313) have been formed and also cyanines from methylnaphthethiazoles. Also compounds containing the chain :CH·N:N· in place of :CH·CH:CH· (*Fuchs and Granang*, B., 1928, 57). Some of these latter are desensitizers towards the photographic plate.

**Neocyanines** contain three quinoline rings attached in positions 1:3:5 in the chain: :CH·CH:C·CH:CH (*Hamer*, J. C. S., 1933, 189; C. and I., 1935, 640). Neocyanine has an Et group attached to each N. It is obtained by the action of ethyl orthoformate on lepidine ethiodide and is a powerful infra-red sensitizer.

Cyanines, with  $\text{C}_6\text{H}_4$   C: group in place of a quino-

line residue, are known, and those with several methyl substituents, e.g. 1:3:3':1':3':3'-hexamethyl-indocarbocyanine chloride is not only a sensitizer but a fast dye for textiles. It is formed from trimethyl-indolenine methiodide and ethyl orthoformate in pyridine solution and is known as **astraphloxine FF**.

## G. Indamine and Indophenol Dyestuffs

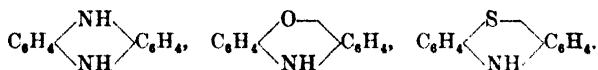
The indophenol and indamine dyestuffs are derivatives of phenylated *p*-quinone mono- and di-imides respectively,  $\text{O:C}_6\text{H}_4\text{:NPh}$  and  $\text{NH:C}_6\text{H}_4\text{:NPh}$  (Chap. XXV, F.).

**Indamines:** **Phenylene blue**,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{C}_6\text{H}_4:\text{NH}_2\text{Cl}$ , obtained by oxidizing a mixture of aniline and *p*-phenylenediamine, when the hydrogen para to the amino group in aniline and three of the four hydrogen atoms of the amino groups of the diamine are removed by oxidation, and union of the two amine residues takes place. **Bindschedler's green** is the corresponding tetramethyl derivative. **Toluylene blue**,  $\text{NMe}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{C}_6\text{H}_2\text{Me}(\text{NH}_2):\text{NH}_2\text{Cl}$ , obtained by oxidizing dimethyl-*p*-phenylenediamine and *m*-toluylenediamine is of interest on account of its relationship to the eurhoidine, neutral red (p. 1045). Indamines are also formed by oxidizing a mixture of an arylamine (or *m*-diamine) with *p*-nitrosodimethylaniline instead of the *p*-diamine.

The **Indophenols** can be formed in a similar manner by oxidizing a mixture of a phenol (or naphthol) with a paradiamine or with *p*-nitrosodimethylaniline. The only dye of technical importance is **indophenol blue**,  $\text{NMe}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}:\text{C}_{10}\text{H}_6:\text{O}$ , obtained by condensing  $\alpha$ -naphthol with *p*-nitrosodimethylaniline. It is sometimes used in combination with indigo, as the process of dyeing is exactly analogous. It is a typical vat dye.

## H. Azine, Oxazine, and Thiazine Dyestuffs

Practically all these dyestuffs are basic dyes, and are used in the form of salts. They are readily reduced to leuco-compounds, which re-oxidize in the presence of air. These leuco-compounds are amino or substituted amino derivatives of dihydrophenazine, phenoxazine, and phenthiazine respectively (Chap. XLV, B.).

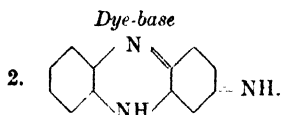
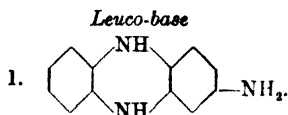


In all cases the amino or substituted amino groups occupy position 2.\*

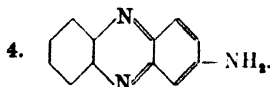
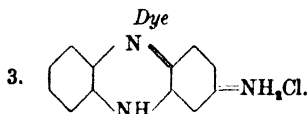
The relationships of the leuco-base (1), dye-base (2), and

\* For purposes of orientating the numbering of the atoms is exactly similar to that in the case of fluorescein (p. 1036) and acridine dyes, the CH in these being replaced by N.

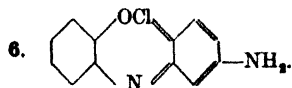
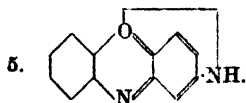
dyestuff (3) are rendered clear by a glance at the formulæ for the azine compounds:



An orthoquinonoid structure for the dye-base and dye is also possible, viz. (4). The oxazine and thiazine dyes can be



represented by formulæ analogous to 3, but with O and S in place of the NH group of the middle ring. If orthoquinonoid formulæ are used for the dye-bases, union between O or S and the substituting NH group in position 4 must be assumed, e.g. (5), but not for the salts, e.g. (6). The orthoquinonoid



formulæ for the salts are now generally adopted; that for the azine salt represents the upper nitrogen in the middle ring, formula 4, as combining with the acid, e.g. HCl, and becoming quinquevalent. Such salts, containing quinquevalent N and tetravalent O or S, are usually termed phenazonium, oxazonium, and thiazonium salts.

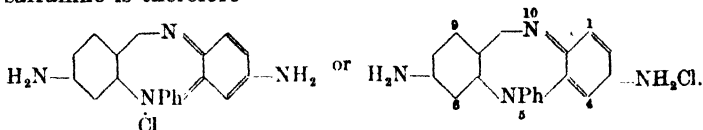
### 1. AZINE DYESTUFFS

1. The azine dyestuffs comprise the following sub-groups:

(a) The **Eurhoidines**.—Most of these are diamino or substituted diamino derivatives, but have no alkyl or aryl group attached to the nitrogen atom in position 5.

(b) The **Safranines** are all 3:7-diamino derivatives, and in addition have a phenyl or substituted phenyl group attached to the nitrogen in position 5. They are phenyl-diamino-phenazonium salts, often with substituents in the benzene

rings or in the amino groups. The formula of the simplest safranin is therefore



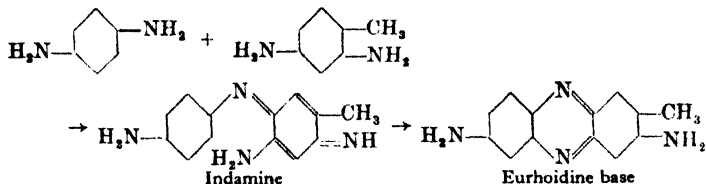
Safranines may also be derived from azines in which one or both of the benzene rings are replaced by naphthalene residues.

(c) The **Aposafranines** also have an aliphyl or aryl group attached to nitrogen in position 5. They are, however, mono-amino derivatives, and always contain one naphthalene residue.

(d) The **Indulines** contain three or four amino groups.

#### (a) THE EURHOIDINES

These form a small and unimportant class. The dye-bases are only weak bases, and form red mono-acid salts. They are usually prepared by the oxidation of indamines. One of the best known is **toluylene red**. By the oxidation of a mixture of *p*-phenylenediamine and *m*-toluylenediamine an indamine (p. 1043) is formed:



**Neutral red**,  $\text{NMe}_2 \cdot \text{C}_6\text{H}_3 \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N(HCl)} \end{array} = \text{C}_6\text{H}_2\text{Me} \cdot \text{NH}_2$ , is obtained by the further oxidation of toluylene blue (p. 1043)

and **neutral violet**,  $\text{NMe}_2 \cdot \text{C}_6\text{H}_3 \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N(HCl)} \end{array} = \text{C}_6\text{H}_3 \cdot \text{NH}_2$ , from *p*-aminodimethylaniline and *m*-phenylenediamine. The constitution of toluylene red follows from the fact that when diazotized and warmed with alcohol it yields a methylphenazine identical with that obtained by oxidizing the methyl-di-

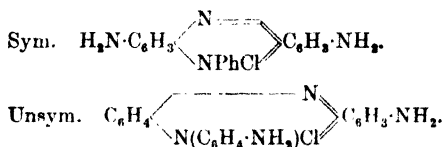


hydrophenazine synthesized from catechol (1:2-dihydroxybenzene) and *m*-toluylenediamine ( $\text{Me}:\text{NH}_2:\text{NH}_2 = 1:3:4$ ).

(b) SAFRANINES

Considerable discussion has taken place with reference to two important points connected with the structure of the safranines, viz.: (1) the ortho- or paraquinonoid structure of the dyes, and (2) the symmetrical or unsymmetrical positions of the amino groups.

*Nielski's* statement of the existence of two isomeric monomethyl safranines was used as an argument in favour of the unsymmetrical arrangement of the two amino groups, but *Körner* and *Schmidt's* proof of the identity of the two compounds lent support to the symmetrical structure which has been since confirmed by *Hewitt*.



By the ordinary methods of diazotizing only one  $\text{NH}_2$  group is removed from safranine, and for some time this was regarded as an argument in favour of the paraquinonoid formula which contains only one true  $\cdot\text{NH}_2$  group. Subsequent experiments have proved that a second amino group can be removed by diazotizing in the presence of concentrated sulphuric acid, and this has given support to the orthoquinonoid formula which contains two free amino groups. The readiness with which the leuco-bases are oxidized to the dye-bases is also in harmony with the ortho structure.

When safranine sulphate is treated with barium hydroxide the green base, safranine hydroxide, is formed, and when this is heated water is eliminated, and a base practically free from oxygen is obtained. This has been urged as an argument in favour of the para constitution, as it involves the elimination of water from  $\cdot\text{NH}_2\text{OH}$  and the formation of  $\cdot\text{NH}$ . With an orthoquinonoid constitution the formation of the anhydro base involves either a molecular rearrangement into the paraquinonoid form followed by loss of water or the elimination of water directly and union between the nitrogen atoms in positions 3 and 5.



**Fast neutral violet B**, 3-dimethylamino-7-ethylamino-5-ethylphenazonium chloride, from *p*-nitrosodimethylaniline and diethyl-*m*-phenylenediamine; **Metaphenylene blue**, 3-dimethylamino-7-tolylamino-5-tolylphenazonium chloride, from the same nitroso compound and di-*o*-tolyl-*m*-phenylenediamine; **Naphthazine blue**, 3-methylamino-7-naphthylamino-5-naphthylphenazonium chloride; **Basle blue R**, 3-dimethylamino-7-tolylamino-5-tolynaphthazonium chloride, is obtained from the nitroso compound and 2:7-ditolynaphthylenediamine,  $C_{10}H_6(NH \cdot C_7H_7)_2$ , and yields the sulphonated dye, **Basle blue S**.

5. Safranines can also be formed by fusing aminoazo compounds with primary arylamines and their salts.

**Naphthyl blue** or **Milling blue**, a diphenylated dinaphthosafranine,  $PhHN \cdot C_{10}H_5 \begin{array}{c} \diagup N \\ \diagdown NPhCl \end{array} C_{10}H_5 \cdot NHPh$ , is formed from

benzeneazo- $\alpha$ -naphthylamine,  $\alpha$ -naphthylamine and aniline hydrochloride, and is used in the form of a sulphonic acid.

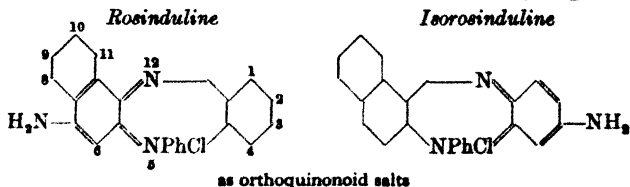
**Magdala red** is a diamono-naphthyl-dinaphthazonium chloride,

$H_2N \cdot C_{10}H_5 \begin{array}{c} \diagup N \\ \diagdown N(C_{10}H_7)Cl \end{array} C_{10}H_5 \cdot NH_2$ , and is used to a certain extent on silk.

The safranines are beautiful crystalline compounds with a metallic green lustre, are readily soluble in water, and dye yellowish red, violet, and blue, and for cotton usually require a tannin mordant.

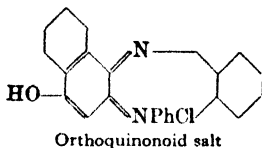
#### (c) APOSAFRANINES. (Cf. p. 1045)

These are usually divided into the **rosindulines** and **isorosindulines**. In the former the amino group is attached to a naphthalene residue, and in the latter to a benzene nucleus. The two groups give respectively red and blue shades. Many contain aliphyl or aryl substituents in the amino group.



The aposafranines are formed by methods exactly analogous to numbers 4 and 5, given under safranines.

**Azocarmine G**, formed by fusing benzeneazo- $\alpha$ -naphthylamine with aniline and its hydrochloride and subsequently sulphonating, is sodium phenylrosindulinedisulphonate. **Azocarmine B** is the sodium salt of the corresponding trisulphonic acid. **Rosinduline 2G**, obtained by heating the acid from Azocarmine B with water at 160°–180°, is the sodium salt of a monosulphonic acid of rosindone, which is the oxygen analogue of rosinduline, e.g.:



**Rosinduline G** is an isomeric monosulphonate, and both compounds are important wool dyes. **Induline scarlet**, prepared by melting the azo derivative of monoethyl-*p*-toluidine with  $\alpha$ -naphthylamine hydrochloride, has ethyl in place of phenyl attached to N in position 5, and methyl in position 3. It is frequently used in conjunction with formaldehyde hydro-sulphite and rongalite for discharging colours.

**Neutral blue**, a typical isorosinduline, contains the NMe<sub>2</sub> in position 2, and is obtained by heating nitrosodimethyl-aniline with phenyl- $\beta$ -naphthylamine.

#### (d) INDULINES

The first induline was prepared in 1863 by *Dale and Caro* by heating aniline hydrochloride with sodium nitrite, and was subsequently (*Martius and Griess*, 1866; *Hoffmann and Geyger*, 1877) shown to be formed by the action of aniline hydrochloride and aniline on aminoazobenzene at 160°. The group comprises blue, violet, and black dyestuffs, which are usually prepared by heating an aminoazo compound with a primary arylamine and its salt, usually under pressure. When a *p*-phenylenediamine is used basic indulines are formed. All the products are insoluble in water, but on sulphonation give water soluble acid dyes.

The formation of aposafranines, safranines, and indulines from aminoazo compounds and monoamine salts probably

proceeds in several stages. In the case of aminoazobenzene itself:

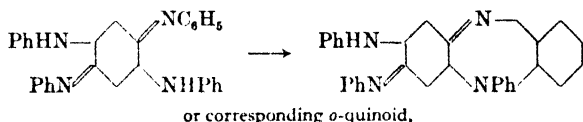
1. The isomerization of the *p*-azo compound to the hydrazone form (cf. p. 467)  $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{N} : \text{N} \cdot \text{C}_6\text{H}_5 \rightarrow \text{NH} : \text{C}_6\text{H}_4 : \text{N} \cdot \text{NHC}_6\text{H}_5$ .

2. Molecular rearrangement during which the  $\cdot \text{NHC}_6\text{H}_5$  group exchanges place with an ortho H atom of the nucleus (Chap. XXII, C2),  $\text{NH} : \text{C}_6\text{H}_4 : \text{N} \cdot \text{NHC}_6\text{H}_5 \rightarrow \text{NH} : \text{C}_6\text{H}_3(\text{NHC}_6\text{H}_5) : \text{NH}$ , whereby an anilo derivative of *p*-quinone is formed.

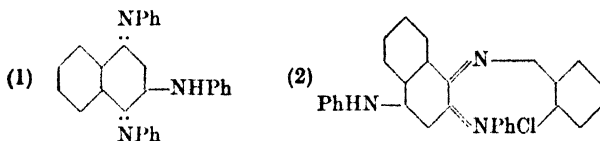
3. The elimination of ammonia from the primary amine and the NH groups, and the formation of quinone anilides,  $\text{C}_6\text{H}_5\text{N} : \text{C}_6\text{H}_3(\text{NHC}_6\text{H}_5) : \text{NC}_6\text{H}_5$ , 2-anilinoquinone-1 : 4-dianilide.

4. The formation of a dianilino derivative, e.g. 2 : 5-dianilinoquinone-1 : 4-dianilide,  $\text{C}_6\text{H}_5\text{N} : \text{C}_6\text{H}_2(\text{NHC}_6\text{H}_5)_2 : \text{NC}_6\text{H}_5$ , by the removal of hydrogen from the quinone nucleus and aniline. This probably occurs at the expense of the aminoazo compound, which becomes reduced to *p*-phenylenediamine.

5. The final condensation of the dianilinoquinone anilide,

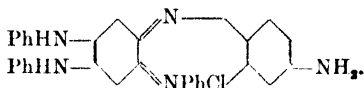


and on further heating more anilino groups are introduced, and various indulines are formed. When benzene azo- $\alpha$ -naphthylamine and aniline hydrochloride are used the anilino dianilide (1) is formed, which condenses to (2):



**Fast blues R or B** are made from aminoazobenzene, aniline, and aniline hydrochloride by heating for different periods; the longer the heating the bluer the shade. They are insoluble and are largely used as pigments for colouring leather, polishes, and for newspaper printing. The final product by prolonged heating is **Induline 6B**, and contains 4 anilino groups in positions 2 : 3 : 7 : 8. The **soluble fast blues** obtained on

sulphonation are important dyes for wool, silk, and can also be used for tannin cotton. The **milling blues** are the sulphonated compounds with naphthalene ring (2 above). The **printing blues**, **acetin blues**, and **laevuline blues** are solutions of the fast blues in ethyl tartaric acid, acetin, and laevulic acid respectively, and are used for cotton printing. **Indamine blue** is a basic dye obtained by using *p*-phenylenediamine instead of aniline, and has the structure:

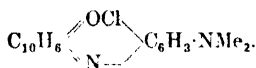


The **nigrosines** are made by heating nitrobenzene or nitrosophenol, aniline, and aniline hydrochlorides with iron filings, and are used for pigments and shoe polishes.

**Aniline black** is probably an azine dye (for structure see *Green, J. S. Dyers*, 1913, 105, 338), and is produced by oxidation of aniline on the fabric.

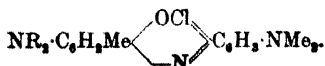
## 2. OXAZINE DYESTUFFS. (Cf. p. 1043)

The first oxazine dyestuff to be manufactured was **Meldola's blue**,

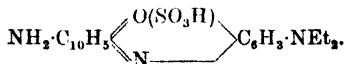


It is obtained by condensing  $\beta$ -naphthol (1 mol.) with an alcoholic solution of *p*-nitrosodimethylaniline, has dyeing properties, but is not fast to alkalis. It is an important leather dye. Blues which are much faster are obtained by condensing **Meldola's blue** with arylamines, thus when condensed with *p*-aminodimethylaniline it yields **new blue B**, which has the  $\cdot\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{NMe}_2$  group in the naphthalene ring in position *para* to the N of the oxazine ring.

**Capri blues**, obtained from nitrosodimethylaniline and dialkyl-*m*-amino-*p*-cresols, are relatively fast,

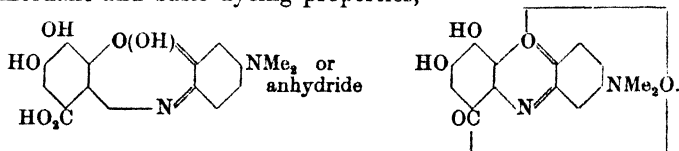


**Nile blue A**, from nitrosodiethyl-*m*-aminophenol and  $\alpha$ -naphthylamine,



**Nile blue 2B**, obtained by using benzyl- $\alpha$ -naphthylamine, contains NHBz in place of  $\text{NH}_2$ .

**Gallocyanine DH**, from nitrosodimethylaniline and gallic acid in boiling methyl alcohol, is an important dye with both mordant and basic dyeing properties,



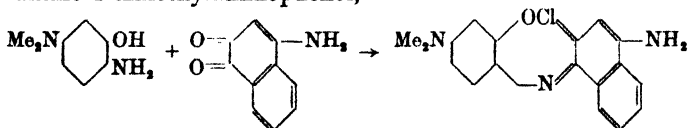
**Prune** is the corresponding methyl ester.

**Delphin blue**, obtained from gallocyanin by the action of aniline and subsequent sulphonation, contains  $\cdot\text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_3\text{NH}_4$  in place of  $\text{CO}_2\text{H}$ .

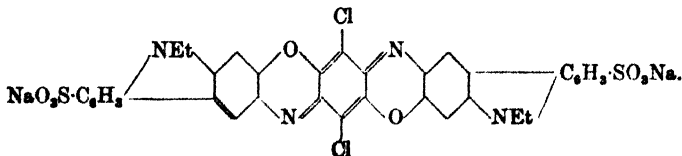
**Gallamine blue paste** has  $\text{CO} \cdot \text{NH}_2$  in place of  $\text{COOH}$  of gallamine.

**Correine RR** is the  $\text{NEt}_2$  analogue of gallamine blue.

A new synthesis of oxazines consists in condensing  $\beta$ -naphthaquinone, or its derivatives, in alcoholic solution with an *o*-amino-*m*-dialkylamino-phenol, e.g. the dimethyl analogue of Nile blue A is obtained from 4-amino- $\beta$ -naphthaquinone and 2-amino-4-dimethylaminophenol,



A brilliant blue direct dye containing two oxazine rings is **Sirius brilliant blue FFR**, obtained by condensing chloranil with 3-amino-N-ethyl-carbazole followed by ring closure by boiling with nitrobenzene and finally sulphonating,



All the latter compounds are mordant dyes, and can be used in the same manner as alizarin.

### 3. THIAZINE DYESTUFFS. (Cf. p. 1043)

*Lauth's* violet (1876), the first member of this group to be prepared, has no commercial value. It is 2:8-diamino-thiazonium chloride,  $\text{NH}_2 \cdot \text{C}_6\text{H}_3 \begin{array}{c} \diagup \text{S} \text{Cl} \\ \diagdown \text{N} \end{array} \text{C}_6\text{H}_3 \cdot \text{NH}_2$ , is prepared by

oxidizing with ferric chloride an HCl solution of *p*-phenylenediamine containing  $\text{H}_2\text{S}$ , and its constitution was established by *Bernthsen*, (A., 1885, **230**, 73) by the following synthesis: Thiodiphenylamine and sulphur give anhydro-thiodiphenylamine. This can be nitrated to a dinitro compound, which can be reduced to the corresponding diamine identical with the leuco-base derived from *Lauth's* violet.

**Methylene blue B**, 2:8-tetramethyldiaminethiazonium chloride, is manufactured by the modern process of oxidizing with dichromate a mixture of dimethyl-*p*-phenylenediamine and dimethylaniline in the presence of sodium thiosulphate and zinc chloride. It is an important dye for tannin cotton, is used as a stain in microscopy, and as the free base finds internal use in medicine.

**New methylene blue N**, obtained by using monoethyl-*o*-toluidine instead of dimethylaniline, is 1:9-dimethyl-2:8-diethylaminethiazonium chloride. **Methylene green G** is the 1-nitro derivative obtained by the action of nitrous and nitric acids on methylene blue B. **Thionine blue** is the trimethylethyl analogue of methylene blue. **Brilliant alizarin blue GR** is

$\text{NMe}_2 \cdot \text{C}_6\text{H}_3 \begin{array}{c} \diagup \text{S}(\text{OH}) \\ \diagdown \text{N} \end{array} \text{C}_{10}\text{H}_3(\text{OH})_2 \cdot \text{SO}_3\text{Na}$ , and **Indochromogene S**,  $\text{NEt}_2 \cdot \text{C}_6\text{H}_3 \begin{array}{c} \diagup \text{S}(\text{SO}_3\text{Na}) \\ \diagdown \text{N} \end{array} \text{C}_{10}\text{H}_3(\text{OH})_2 \cdot \text{SO}_3\text{Na}$ , is ob-

tained by condensing *p*-aminodiethylaniline with 1:2-naphthaquinone-4:6-disulphonic acid in dilute alkaline solution.



## I. Hydroxyketone Dyestuffs

The following hydroxyketones act as dyestuffs:

**Alizarin yellow C** (gallacetophenone), 2:3:4-trihydroxyacetophenone, is obtained by heating pyrogallol with acetic acid. **Alizarin yellow A** is the corresponding trihydroxybenzophenone. **Lawson**, 2-hydroxy-1:4-naphthaquinone, is the common henna dye for hair, and 1:3:4'-trihydroxyflavone (Chap. LXIV, B.), known as **Apigenin**, is present in camomile and is also used as a hair dye. **Alizarin black S** is 1:2-dihydroxy-5:8-naphthaquinone or naphthazarine (p. 575), but the best-known members are the hydroxyanthraquinone or **alizarin** dyes (Chap. XXXII, A.).

These are all phenolic substances, and hence acid dyes; they all contain two hydroxyls in ortho positions. On cotton they are used as mordant dyes, i.e. for forming co-ordinated **lakes** with Cr, Al, Fe, &c., on the fabric. They are relatively fast colours, but have been replaced to a certain extent by the fast azo acid dyes and the azo mordant dyes (cf. this Chap., B.) for wool. The colour produced depends not only on the particular dye used but also upon the mordant.

Alizarin is made by fusing anthraquinone-2-sulphonic acid with alkali and chlorate. When the 2-acid is further sulphonated, a mixture of 2:6- and 2:7-disulphonic acids is formed; the two acids can be separated by means of their sodium salts, and when fused with alkali the former yields 1:2:6-trihydroxyanthraquinone, **flavopurpurin** or alizarin X, and the latter the 1:2:7 isomeride known as **anthrapurpurin**. The 1:2:4 compound known as **purpurin** is found in madder, and can be obtained by oxidizing alizarin with sulphuric acid and  $\text{MnO}_2$ . The 1:2:3 compound, **anthracene brown** (anthragallol), is obtained by condensing benzoic and gallic acids in sulphuric acid solutions, and is usually accompanied by some 1:2:3:5:6:7-hexahydroxyanthraquinone or **anthracene brown SW**.

**Alizarin bordeaux B**, 1:2:6:8-tetrahydroxyanthraquinone, is obtained by oxidizing alizarin with fuming sulphuric acid, and hydrolysing the resulting sulphonic acid with 80 per cent acid, and when oxidized with sulphuric acid and  $\text{MnO}_2$  it yields **anthracene blue WR**, 1:2:4:5:6:8-hexahydroxyanthraquinone.

Numerous sulphonic acids, obtained by heating the above-

mentioned dyestuffs with fuming sulphuric acid, are known. Alizarin itself yields **alizarin red S** or **alizarin carmine**, sodium 1 : 2-dihydroxyanthraquinone-3-sulphonate. **Alizarin garnet** is 1 : 2-dihydroxy-4-amino-anthraquinone, and is obtained by nitrating alizarin dibenzoate, hydrolysing and reducing with sodium sulphide. **Alizarin SSS** is sodium 1 : 2 : 6-trihydroxyanthraquinone-sulphonate. These are acid dyes.

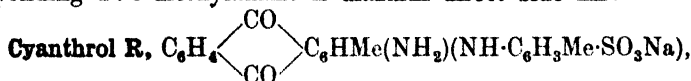
Simple alizarin derivatives used as dyes are the 3-nitro (**alizarin orange**), 3-amino (**alizarin maroon**), and the 4-amino (**alizarin garnet**).

Numerous amino- or aryl- amino-anthraquinones are formed by the simple reaction between hydroxyanthraquinones and ammonia or arylamines, especially in presence of boric acid, and form an extremely important group of dyestuffs, including their sulphonic acid. **Purpurin** (1 : 2 : 4-trihydroxy) yields 1-amino-2 : 4-dihydroxyanthraquinone.

Quinizarin (1 : 4-dihydroxy) and *p*-toluidine give 1-hydroxy-4-tolylamino-anthraquinone, the 2'-sulphonic acid of which is **alizarin isol**, and this gives violet blue shades on chrome mordanted wool. Quinalizarin (1 : 2 : 5 : 8-hydroxy) and *p*-toluidine yield **alizarin viridine**, 1 : 2-dihydroxy-5 : 8-di-*p*-tolylamino-anthraquinone, which gives green shades on chrome mordanted wool.

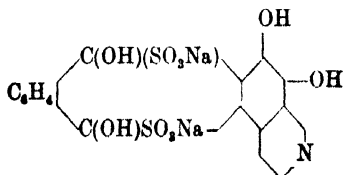
**Quinizarin green** is obtained by the action of *p*-toluidine or 1 : 4-dichloroanthraquinone and subsequent sulphonation.

A more complex alizarin dye is **alizarin sapphirol B** (**Solway blue**). Anthrarufin (1 : 5-dihydroxy) sulphonated yields the 2 : 6-disulphonic acid, and this nitrated gives 4 : 8-dinitro-1 : 5-dihydroxyanthraquinone-2 : 6-disulphonic acid, which on reduction yields the corresponding diamino-compound the sodium salt of which is alizarin sapphirol B. This gives pure blue shades on wool from an acid bath, and with a chrome mordant green blue shades very fast to light. The corresponding 4 : 8-diethylamine is **alazarin direct blue EB**.

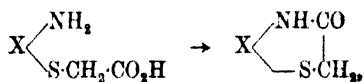


is formed from 2-methylantraquinone, nitrating to the 1-nitro-compound, reducing to the 1-amine, bromination to the 4-bromo-compound, replacing the bromine by the *p*-tolyl-amino group, and finally sulphonating.

**Alizarin blue**, obtained by heating 3-nitroalizarin and the corresponding amino-compound with glycerine and sulphuric acid, has a pyridine nucleus condensed in position 3:4, and with bisulphite gives the disulphonic acid **alizarin blue S**,



All anthraquinones with  $\cdot\text{NH}_2$  and  $\cdot\text{S}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  in ortho positions are water soluble, and can dye wool from a sodium acetate bath, and then by treatment with hot dilute acid the soluble compound is converted into the coloured insoluble lactam,



pigments fast to washing and milling.

## J. Sulphide Dyestuffs

The first dyestuffs of any importance to be manufactured were **vidal black**, obtained in 1893 by fusing *p*-aminophenol with sulphur, and **fast black B** from 1:8-dinitronaphthalene and sulphur. Since that time numerous yellow, brown, green, blue, and black dyes have been obtained by treating various compounds, e.g. aminohydroxyphenazines, with sodium polysulphide.

*Fierz-David* (J. Soc. Dyers, 1935, 50) concludes that many of these contain several thiazine groups united by  $-\text{S}-$



group or several such groups, or by these and  $-\text{S}-$  or  $-\text{S}-\text{S}-$  groups.

## K. Vat Dyestuffs

This is the name given to a series of insoluble dyestuffs which can be reduced to alkali soluble leuco-compounds. Many of the leuco-compounds are now sent out in stable solid forms, e.g. seledon colours. The fabric is immersed in the solution of the leuco-compound, which is then oxidized, usually by atmospheric oxygen, to the dyestuff on the fibre. They contain the :CO or :CS group, which yield :CH·OH or :CH·SH on reduction.

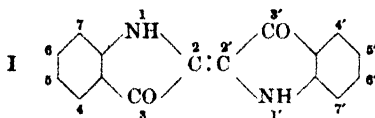
The two main sub-groups are:

- I. Indigoid vat dyestuffs.
- II. Anthraquinone vat dyestuffs.

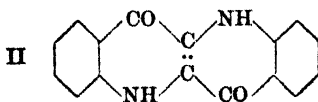
### I. INDIGOID VAT DYE STUFFS

The best known of these is indigo itself, and this has been dealt with in Chap. XLI, C. From many points of view the indigo question is one of interest to chemists. Within recent years the synthetic product has replaced, to a large extent, the natural dye. This is clear from the fact that the acreage under cultivation in India had fallen from nearly 1,500,000 acres in 1893 to about 150,000 in 1914. The War revived interest in the natural product, and in 1917 about 750,000 acres were under cultivation, but this acreage has again fallen.\* According to *H. E. Armstrong*, the synthetic dye is inferior in dyeing properties to the natural product, owing to the presence of other dyes in the latter.

For reference the following system of numbering is used:



For alternative formula II, cf. *Robinson*, C. and I., 1933, 137.

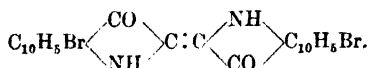


\* Cf. Chap. XII in *Gardner's The British Coal Tar Industry*.  
(B 480)

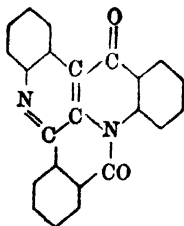
By direct bromination it is possible to replace from one to 6 atoms of hydrogen in the following order: 5, 5', 7, 7', 4, 4'. 6:6'-Dibromoindigo, obtained from 4-bromo-2-aminobenzoic acid, is identical with one of the constituents of the ancient **Tyrian purple**. Chloro-derivatives may be prepared from chlorinated phenylglycine-carboxylic acids. The halogenated indigos are brighter and much faster to bleaching agents than indigo itself. **Ciba blue 2B**, or 5:5':7:7'-tetrabromoindigo is a dye of considerable commercial importance. The corresponding tetrachloro compound is **brilliant indigo B**, and the 4:4'-dichloro-5:5'-dibromoindigotin is **brilliant indigo 4G**. The introduction of other groups, e.g. amino, alters the colour, thus **Ciba brown R** is the tetrabromo-6-6'-diamino-indigotin.

Indigo derivatives can be synthesized by condensing isatin with compounds containing reactive methylene groups, e.g. benzocoumarone.

The corresponding naphthalene homologues of indigo can be synthesized from  $\alpha$ - and  $\beta$ -naphthylamines by the chloroacetic acid method. They are somewhat fugitive green dye-stuffs; the  $\beta$ -compound when brominated gives a dibromo derivative known as **Ciba green G**,

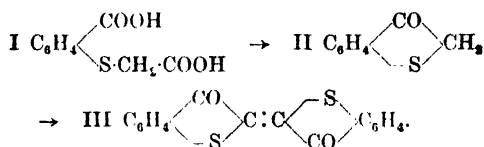


**Indigo yellow 3G** from benzoylated indigotin and alkali; it is important, as when used in the same vat with indigo it gives uniform shades of green. It has been shown (1932) to have the structure



The **thioindigos** are compounds of commercial importance (*Friedlander*, 1905), and contain two S atoms in place of the two NH groups. The numbering is the same (cf. p. 1057), the two S atoms being 1 and 1'. **Thioindigo red B** (III), the parent compound, is obtained by alkali fusion of phenylthioglycollic-o-

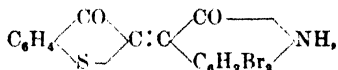
carboxylic acid I, and oxidizing the resulting thioindoxyl (II) with potassium ferricyanide:



Numerous halogenated, alkylated, and amino-derivatives of this compound have been prepared. An interesting synthesis of thioindigo red is by condensing acetylene dichloride with sodium thiosalicylate to acetylene-bis-thiosalicyclic acid,  $\text{CO}_2\text{Na}\cdot\text{C}_6\text{H}_4\cdot\text{S}\cdot\text{CH}:\text{CH}\cdot\text{S}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H}$ , which readily loses water yielding the dye. Corresponding derivatives of the naphthalene series are also known.

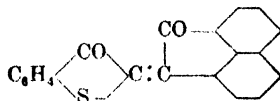
The colours of the thioindigo compounds vary not only with the substituents but with their positions. Thus in the 5:5'-positions they tend to deepen the shade, but in 6:6'-positions to lighten it. **Indanthrene brilliant pink R**, 6:6'-dichloro-4:4'-dimethylthioindigo, is a brilliant dye with remarkable fastness.

An important member is **Ciba red G** or **Thioindigo scarlet G**, 2'-thionaphthene-5:7-dibromo-3-indolindigo,



and is obtained by condensing isatin with  $\alpha$ -hydroxythionaphthene and brominating.

**Ciba scarlet G** is 2'-thionaphthene-acenaphthene indigo and



is obtained by condensing acenaphthaquinone with hydroxythionaphthene.

**Ciba violet** has one NH and one S, and is intermediate between indigo and thioindigo. It is obtained by condensing isatin- $\alpha$ -anilide with thioindoxyl, and its tribromo-derivative is **Ciba violet B**.

## II. ANTHRAQUINONE VAT DYESTUFFS

These comprise some of the fastest dyes known, and their use has increased enormously within recent years, e.g. a comparison of 1928 with 1913 shows an increase in the British consumption of 174 per cent as compared with an increase of 32 per cent for all classes of dyestuffs. This increased use has added to the importance of the anthracene and anthraquinone industries. The dyestuffs are conveniently divided into the 5 groups:

1. **Acylaminoanthraquinones.**
2. **Anthraimides** (polyanthraquinoylamines).
3. **Hydroazines.**
4. **Complex cyclic quinones.**
5. **Anthraquinone acridones.**

They are all derivatives of anthraquinone, and as vat dyes are converted into leuco-compounds ( $>\text{CO} \rightarrow >\text{CH}\cdot\text{ONa}$ ) by alkaline hydrosulphite. The vats from which the dyeing takes place are not colourless—as in the case of indigo—but deeply coloured, and the dye is developed by oxidation on the fibre.

*Soluble anthraquinone dyes.*—By the action of fuming sulphuric acid or chlorosulphonic esters with a reducing metal and a tertiary base the dye is converted into the acid sulphuric ester of the leuco-compound  $>\text{CH}\cdot\text{O}\cdot\text{SO}_3\text{H}$ . These products are placed on the market in the form of pastes (**Soledon colours**) each corresponding with a **Caledon dyestuff**. They are soluble in water, and the solution dyes wool, silk, and cotton direct from a sodium sulphate bath. The colour is finally developed by hydrolysis and oxidation with cold nitrous acid or acid dichromate. Indigoid dyes can be treated similarly.

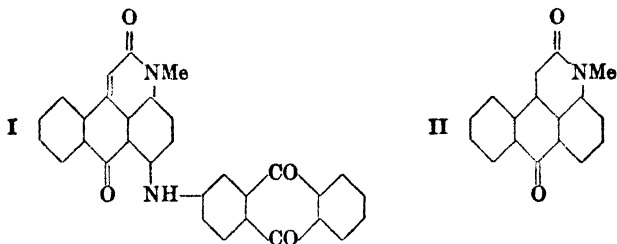
1. **Acylaminoanthraquinones.**—**Argol yellow 1NG**, 1-benzoylamino-anthraquinone,  $\text{C}_6\text{H}_4(\text{CO})_2\cdot\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{COPh}$ , dyes cotton fast yellow shades from a hydrosulphite bath. Numerous other aroylamino compounds are known, and are generally termed **argol colours** or more commonly as **Indanthrene dyes**. They are often prepared by the reaction between the acid and the amine, and are generally used in a dilute alkaline bath to prevent hydrolysis of the aroyl group.

Succinic acid yields **Argol yellow 3G**, 1:1'-succinylo-amino-anthraquinone.

2. **Anthraimides** containing two anthraquinone residues united by a **NH** group, e.g. **Indanthrene orange 6BTK**,

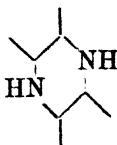
$C_6H_4(CO)_2 \cdot C_6H_3 \cdot NH \cdot C_6H_3(CO)_2 \cdot C_6H_4$ , prepared by the condensation of 2-chloro- with 1-amino-anthraquinone. Better known are the trianthraquinonylamines with two NH groups, e.g. **Bordeaux 3B**, di-4'-methoxy-1-anthraquinonyl-2:6-diamino-anthraquinone,  $C_6H_4(CO)_2 C_6H_2(OMe) \cdot NH \cdot C_6H_3(CO)_2 C_6H_3 \cdot NH \cdot C_6H_2(OMe)(CO)_2 C_6H_4$ , and **Indanthrene red R**, di-1-anthraquinonyl-2:7-diamino-anthraquinone.

The complex dye **Algol red B, I**, is formed in the follow-

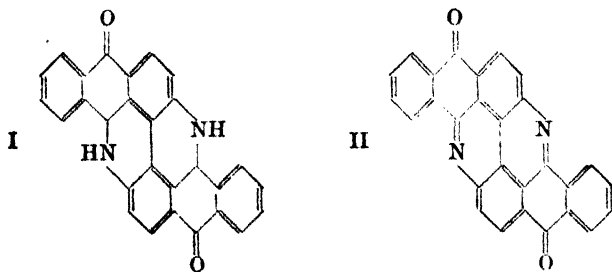


ing stages: 1-chloroanthraquinone  $\rightarrow$  1-methylaminoanthraquinone  $\rightarrow$  acetyl derivative ( $\cdot NMeAc$  in I)  $\rightarrow$  ring closure by aid of alkalis to N-methylanthraquinone pyridone, II,  $\rightarrow$  bromination in 4 position  $\rightarrow$  replacement of Br by 2-aminoquinonyl group.

3. **Hydroazines** contain the group



attached to two anthraquinone groups, e.g. **Indanthrone, I**, N-dihydro-1:2:1':2'-anthraquinoneazine, known as **Indanthrene blue R**, **Caledon blue R** or **Duranthrene blue**.\*



\* The names Indanthrene, Caledon and Duranthrene are used by different makers to denote the same dyestuff.

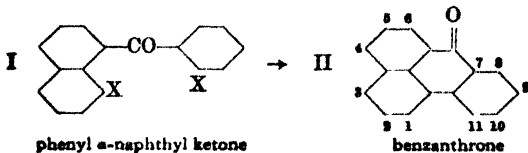


It is the oldest and one of the most important members of the group, and is manufactured by heating 2-aminoanthraquinone with potash and potassium nitrate. Its structure has been proved by synthesis, e.g. condensation of 1 : 2-diaminoanthraquinone with 1 : 2-dibromoanthraquinone, or *Ullmann's* condensation of 2 mols. of 1-amino-2-bromoanthraquinone with copper powder. It is extremely stable to temperature, acids and alkalis, and with hydrosulphite yields a blue vat consisting of the disodium salt (two  $\cdot\text{CH}\cdot\text{ONa}$  in one ring), and is used for dyeing cotton from a strong alkaline vat and is faster to light and washing than indigo. Its halogenated products have greener shades.

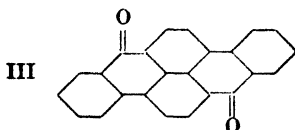
Its oxidation product (2N in place of 2NH) 1 : 2 : 1' : 2'-*anthraquinoneazine* II is known as **Flavanthrone** or **Indanthrene yellow G**, and is formed when 2-aminoanthraquinone is fused with potash at  $330^{\circ}$ – $350^{\circ}$ , or better, by heating the amine with  $\text{PCl}_5$  in boiling nitro-benzene. It dyes cotton a brilliant yellow from a purple-blue vat, but shows a tendency to become reduced on exposure to light to indanthrone, but is used for producing green shades by admixture with blue vat dyes.

4. **Complex quinones.**—Anthraquinone itself is not a mordant dye but its 1 : 2-dihydroxy derivatives are. On the other hand, certain complex cyclic quinones have dyeing properties in the absence of hydroxyl groups. They are not mordant dyes like alizarin but vat dyes, and are dyed from the reduced dye vat. The essentials for the producing of dyeing properties are: (a) the presence of at least two carbonyl groups joined by a conjugated system of olefine links; (b) the condensed rings must contain either the pyrene or perylene structure (Chap. XXXII, C.), i. e. most rings must be condensed with more than two other rings.

A common method for the formation of some of these compounds is by the cyclization of C-aryl derivatives of naphthalene or anthracene with aluminium chloride or sulphuric acid. A new 6-carbon ring is formed (II) by union of the *ortho* C atom of the aryl group of the  $\cdot\text{COAr}$  complex with the second *peri* position in the naphthalene molecule (marked X and X in I).

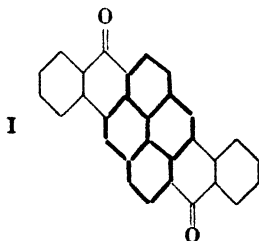


Similarly, the dibenzoyl  $\alpha$ -dinaphthyl gives dibenzanthrone (p. 1064), and benzoylbenzanthrone yields dibenzpyrene-quinone III.

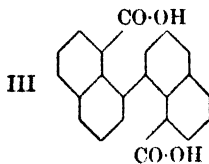
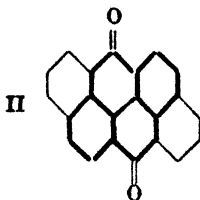


Among some of the commoner dyes are:

1. **Pyranthrone\* I** is known in the industry as **Indanthrene golden orange G**, and is an extremely fast orange dye yielding a purple-red hydrosulphite vat. It is usually made from dimethyl-dianthraquinonyl by heating at  $350^{\circ}$ – $380^{\circ}$ , by fusing with zinc chloride at  $280^{\circ}$ , or by heating with caustic soda and alcohol at  $150^{\circ}$ , and its structure follows from its formation from dibenzoylpyrene by cyclization with  $\text{AlCl}_3$  at  $160^{\circ}$ . Its halogen derivatives give redder shades.

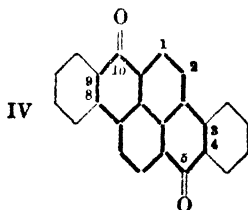


2. **Anthanthrone II** is formed by the action of sulphuric acid or  $\text{AlCl}_3$  on the 2:2'- or 8:8'-carboxylic acid of 1:1'-dinaphthyl III. It is used mainly in the form of its halogen derivatives, e.g. the dichloro-compound is **Indanthrene brilliant orange GK** and **RK**.

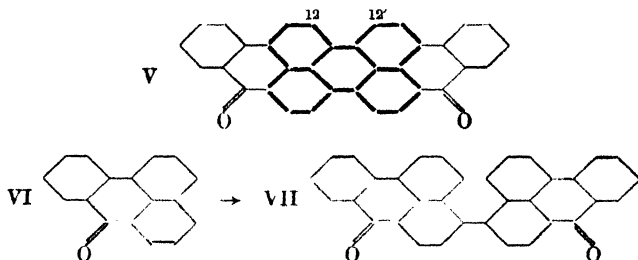


\* Certain rings are emphasized in order to show the pyrene structure present in the molecule.

3. **Dibenzpyrenequinones**, especially the 3:4:8:9-dibenzpyrene-5:10-quinone IV, which is known as **Indanthrene golden yellow GK**, and its dibromo derivative as **RK**.



4. **Dibenzanthrone**. The 2:2':13:13'-dibenzanthrone V is a dark-blue vat dye known as **Indanthrene dark-blue BO**. It is made from benzanthrone VI, and caustic soda at 230°-240°, an intermediate being dibenzanthronyl VII, and

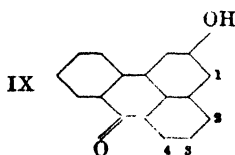


its structure follows from its formation from 4:4'-dibenzoyl-1:1'-dinaphthyl VIII and  $\text{AlCl}_3$ . Chlorination yields **Indanthrene violet RT**, and nitration and reduction yields aminodibenzanthrone or **Indanthrene green B**, and this on oxidation with sodium hypochlorite gives the fastest black known, viz. **Indanthrene black BB**.



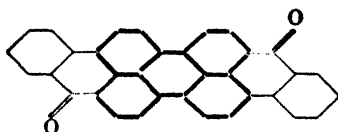
A better method for making dibenzanthrone is by heating benzanthrone with alcoholic potash at 100° and fusing the resulting 2:2'-dibenzanthranoyl with potash or oxidizing it in acid liquor. Benzanthrone with manganese dioxide and

sulphuric acid at 0° gives 13:13'-dibenzanthranoyl, together with some 12-hydroxybenzanthrone (IX),

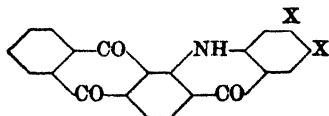


The corresponding 12:12'-dihydroxydibenzanthrone, obtained by oxidizing dibenzanthrone in the same way, is valueless as a dye, but its *dimethyl ether*, formed by methylation with methyl sulphate in nitro-benzene, is **Caledon jade green**, which gives a brilliant blue-green shade and is one of the fastest dyes known. Its structure follows from its formation from 12-hydroxybenzanthrone by methylating and fusing the methyl ether with potash at 180°. The ethylene ether ( $\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{O}\cdot$  in place of  $2\text{CH}_3\text{O}\cdot$ ) is an important blue dye.

5. **Isodibenzanthrone**, obtained by the condensation of 13-chlorobenzanthrone with potash, is known as **Indanthrene violet R extra** (*Caledon purple R*).

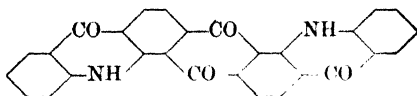


6. **Anthraquinone acridones**, 2:1-anthraquinoneacridone, 1-chloroanthraquinone and anthranilic acid in presence of copper powder and sodium acetate yield 1-anthraquinonyl-N-anthranilic acid, which gives the acridone with sulphuric acid



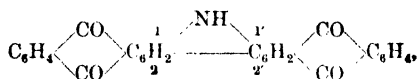
or  $\text{AlCl}_3$ . It is a fast dye with a weak violet-red shade. The dichloro compound with chlorine in positions X is **Indanthrene red-violet R.R.K** and is the best vat dye for pink shades.

## 2 : 1 : 6 : 5-Anthraquinone-bisacridone,



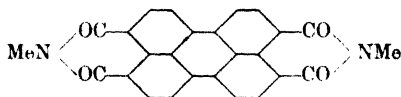
is **Indanthrene violet BN**.

The carbazole derivative,



obtained by oxidizing 1 : 1'-dianthraquinonylamine, is a fast yellow dye. Similar carbazole compounds, obtained by condensing 2 mols. of phthalic anhydride with N-ethylcarbazole, with Et attached to N and carbazole ring in 2 : 3 and 2 : 3'-position, is **Hydron yellow G**.

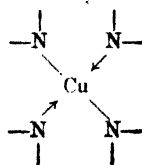
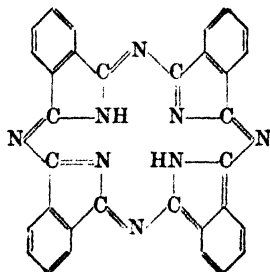
The compound



is the bright-red dye **Caledon red GG**, obtained by fusing 1 : 8-naphthalene-imide with potash and methylating the diimide of perylene-3 : 4 : 9 : 10-tetracarboxylic acid so formed.

## L. Phthalocyanines

These form a group of pigments the discovery of which was based on the observation that by passing ammonia into crude phthalimide contained in an iron pot a dark-blue by-product is formed. The parent substance phthalocyanine has been shown by *Linstead* and others (J.C.S., 1934, 1016) to have the structure



A good yield of copper-phthalocyanine is formed from phthalonitrile,  $o\text{-C}_6\text{H}_4(\text{CN})_2$  (4 mols.), and copper (1 at.) and has the copper attached to the 4 central N atoms in the above formula. It replaces 2 hydrogen atoms, and is thus attached to 2 N atoms by covalent links and to the other two by coordinate links, i.e. each of the two nitrogen atoms gives a lone pair of electrons to the copper atom.

The metallic phthalocyanines are characterized by their intense reddish- to greenish-blue colour, by their great stability, e.g. the copper compound sublimes at  $550^\circ\text{--}580^\circ$  and is unaffected by concentrated sulphuric acid. The structure given above has been confirmed by *Robertson's* X-ray study of the crystal structure (J. C. S., 1935, 615; 1936, 1195). The compounds crystallize extremely readily, and the H, Cu and Ni compounds are all isomorphous. The copper compound is also formed by heating *o*-halogenated benzonitriles or benzamides with cuprous cyanide, and the lead compound, a bright-green pigment, by heating phthalonitrile with lead or lead carbonate. The phthalonitrile can be obtained by treating phthalimide with phosgene in pyridine or dimethylaniline solution.

They are valuable pigments in the plastic, varnish, paper and rubber industries. For use they are generally ground in the presence of a water soluble dispersing agent such as sulphonated oils or sulphated higher fatty alcohols.

### M. Acetate Cellulose Dyes

In the rayon fabrics of the acetylcellulose type, e.g. celanese, no free hydroxyl groups are present, and they cannot be dyed with direct cotton dyestuffs, but can take up coloured substances with neutral, feebly basic or feebly acidic properties, especially those soluble in organic solvents but sparingly soluble in water. Hence the dyeing process is regarded as a case of solid solvent rather than chemical activity. The shot-silk effects are produced by using a rayon fabric with a viscose warp and celanese weft, using a combination of a direct cotton dyestuff with an acetate silk dyestuff. Important groups of acetate silk dyes are:

1. **Ionamines** (*Green and Saunders*, 1922) or amino-azomethyl-omega sulphonates,  $\text{X}\cdot\text{N}:\text{N}\cdot\text{Y}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{SO}_3\text{Na}$  or

$X:N:N\cdot Y\cdot NR\cdot CH_2\cdot SO_3Na$ , obtained by coupling diazonium salts with methyl-omega sulphonic acids of primary and secondary amines (J. S. D. Col., 1923, 10; 1924, 138). In the hot dye bath in contact with the fibre they slowly undergo hydrolysis, especially in the presence of a small amount of free acid or alkali, giving formaldehyde bisulphite and the free amino-azo compound  $X\cdot N_2\cdot Y\cdot NH_2$  or  $X\cdot N_2\cdot Y\cdot NHR$ , which is taken up by the fibre. The amino-azo compound so formed can be utilized direct or can be diazotized on the fabric and coupled with phenols, especially 2-hydroxy-3-naphthoic acid. **Ionamine B** is obtained by coupling *p*-nitrophenyldiazonium chloride with aniline-methyl-omega sulphonic acid (sulphomethylaniline),  $NO_2\cdot C_6H_4\cdot N_2\cdot C_6H_4\cdot NHCH_2\cdot SO_3Na$ , and **Ionamine black AS** is the corresponding dimethylamine compound with  $NMe_2$  in place of  $NO_2$ .

2. **Dispersol Dyes**.—Unsulphonated azo dyes, e.g. soudans, oil yellows, have a certain affinity for acetate silk fibres, but as they are insoluble they are rendered into a colloidal state by means of a sulphonated oil, e.g. sulphonated ricinoleic acid. **Dispersol yellow 3GS** is obtained by coupling benzenediazonium chloride with 1:3-dihydroxyquinoline and emulsifying.

3. **Duranol dyes**, which are faster than most azo dyes, are unsulphonated amino derivatives of anthraquinone in colloidal suspension, e.g. with the condensation product of formaldehyde with naphthalene-sulphonic acids and subsequently neutralizing with ammonia. 1-Amino-anthraquinone gives yellow, the 1:5-diamino red, and the 1:4-diamino-compound crimson shades, and diaminoanthrarufin gives a blue shade. Also amino-anthraquinone with  $CO_2H$  or  $SO_3H$  ortho to  $NH$  or  $NH_2$  group or sulphonic acids from amino-anthraquinones may be used.

## N. Pigments

Insoluble organic colouring matters are replacing to a certain extent the older inorganic pigments, although on the whole they are not so resistant to light and air. They may be used either for the manufacture of a paint or for incorporation with rubber or the newer plastics, and require to be reduced to a very fine state of division by milling.

Among the older substances are Prussian blue, the eosins

deposited on basic lead acetate, and the alizarin lakes. More recently the lakes formed from triphenylmethane dyes with phosphomolybdo-tungstic acid have come into use under the names of *Fanal* and *Eular*, colours which are extremely fast, and still more recently the phthalocyanines and the chrome lakes of azo dyes.

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## LX. PLASTICS \*

This term comprises many different types of compounds, both natural and synthetic, characterized by their being pliable or capable of being moulded and yet by suitable treatment, e.g. heat or chemical reagents, being transformed into extremely hard and sometimes brittle substances. Rubber belongs to this group but has been dealt with in another chapter. It differs from other plastics in its marked elasticity. No field of organic chemistry has made more rapid advances during the period 1926-39.

The more common types of plastics may be grouped in the following main classes: I. Bitumens. II. Natural Resins. III. Synthetic Resins, including polymerization resins, bakelites, urea formaldehyde resins, casein or lactoid resins, and cellulose ester and ether plastics.

### A. Bitumens

These are natural dark-coloured resins found mainly in the Rocky Mountains, and were used for moulding and electrical insulators, but have been largely replaced by Bakelite. Bitumen was used by the Egyptians for impregnating the wrappings of mummies.

\* 1. *Synthetic Resins and Applied Plastics*. Edited by R. S. Morell (London, Oxford Univ. Press, 1937).

2. "The Approach of Plastics to Rubber," Barron, C. I., 1938, 652.

3. *Artificial Resins*, Scheiber and Sandez. Trans. by Fyleman.

4. *Chemical Structure of Plastics*. C. I., 1942, 201.

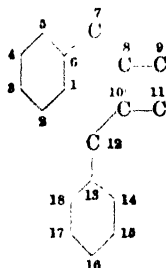


## B. Natural Resins \*

This constitutes a group of many different substances used in different industries. The commonest is ordinary resin, which has been dealt with in Chap. XXXII, B3. Another extremely important resin is **Shellac**, manufactured from East Indian lac, an exudation from the lac insect (*Tacchardia lacca*), which grows on certain species of jungle trees. Some 20,000 tons are manufactured per annum, and it is largely used for high-grade varnishes and lacquers and also for gramophone records of the rigid type. Other resins are *copal*, *dammar*, *dragon's blood* and *amber*, and numerous others. Many have been investigated, but their exact composition and structures have not been determined (cf. J. C. S., 1935, 633, 1576).

### Lignanes

The wood, rhizomes, seeds, oils and resins of many plants yield products containing a  $C_6-C_3$  skeleton or a dimeride of this. The simplest example is isopropyl benzene, the skeleton of which is found in safrole and eugenol; cinnamic, ferulic and caffeic acids also contain the  $C_6-C_3$  skeleton. The term lignane has been given to the hydrocarbon with 2  $C_6-C_3$  complexes united by the  $\beta$ -carbon atom of the  $C_3$  chain,



and this is the parent substance of the components of many natural resins. By union between  $C_1$  and  $C_{12}$ , a 1-phenyl-naphthalene derivative is formed.

\* For statistics, cf. C. and I., 1937, 439. In G. B. value £7,250,000 in 1935.

*Guaiaretic acid*,  $C_{20}H_{24}O_4$ , the chief constituent of guaiacum resin, has been shown to be 9:11-dimethyl-3:16-dihydroxy-4:15-dimethoxy- $\Delta^{8:10}$  lignane (*Haworth* and others, J. C. S., 1934, 1423; 1935, 120). *l*-Matairesinol,  $C_{20}H_{22}O_6$ , from the heartwood of *Podocarpus spicatus* (matai), has the two OH and two OMe in the same position as in guaiaretic acid, but has no olefine link and has carbons numbered 8 and 10 united by

the  $\cdot CO \cdot O \cdot CH_2$  forming the ring  $\begin{array}{c} 8CH \cdot CO \\ | \\ 10CH \cdot CH_2 \end{array} \begin{array}{l} \diagup \\ \diagdown \end{array} O$ . *l*-Hinokinin,  $C_{20}H_{18}O_6$ , from the resin of Japanese cypress (*Cupressus obtusa*),

is the methylenedioxy analogue of matairesinol, two  $CH_2 \begin{array}{l} \diagup \\ \diagdown \end{array} O$  in place of two OMe, OH groups. *Cubebin*,  $C_{20}H_{20}O_6$ , from the unripe fruit of *Piper cubela*, has the two methylenedioxy groups and a CHO group in position 9 and a  $CH_2OH$  in position 11. *Conidendrin*,  $C_{20}H_{20}O_6$ , from European spruce (*Picea abies*), Japanese hemlock (*Tsuga sicholdii*) and also waste sulphite liquors in chemical pulp factories, is analogous to matairesinol but with a union between  $C_1$  and  $C_{18}$  (cf. *Haworth*, Rep., 1936, 270 *et seq.*).

### C. Synthetic Resins \*

The synthetic resin industry is rapidly becoming an important factor in world commerce ("The Rise of the Plastics Industry", *F. Sproston*, C. and I., 1938, 607). The production in 1934 is estimated at about 70,000 tons, valued at 6 million pounds. The chief class is the phenolformaldehyde type followed by the glyptal. The output of natural resins is estimated at about 750,000 tons, of which 80 per cent is colophony and 18 per cent shellac. The synthetic resins vary enormously in properties: the colour varies from complete transparency to opaque black, and in texture from soft to hard, tough to friable, and brittle to elastic. They are all non-crystalline, and X-ray examination shows only a limited degree of structural regularity. They closely resemble glass, and are hence sometimes termed "organic glasses". There are two main types, viz.:

\* For statistics, cf. C. and I., 1938, 3.

1. *Thermoplastic*, which soften when heated and harden again on cooling, and which dissolve in certain solvents. They are probably long-chain compounds practically uniplanar. Examples are the polymerized olefines, vinyl plastics, novolak resins.

2. *Thermo-hardening resins*.—These are plastic when formed, but when heated become hard and non-soluble. They are not softened on reheating, and include bakelite resins, urea-formaldehyde resins, glyptals.

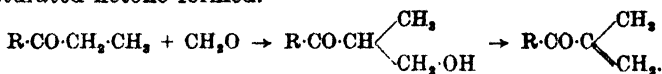
### 1. POLYMERIZATION RESINS \*

These are colourless, transparent or semi-transparent polymerization products of such unsaturated compounds as coumarone, indene, styrene, itaconic acid, vinyl halides, esters and ethers, acryl compounds and methylene ketones, all of which are characterized by containing at least one vinyl group,  $>\text{CH}:\text{CH}_2$ . As a rule most of the products have low softening points, and also absorb water to a certain extent. They are clear, resilient, and can be turned on a lathe, and are also excellent for use as an inner layer in the manufacture of triplex glass or as a glass substitute, and for fountain-pen reservoirs, also for varnishes and linoleum.

The vinyl compounds are usually made from acetylene by addition of hydrogen halide (cf. Duprene, Chap. LXI, E3), acetic acid or chloracetic acid, using a mercury salt catalyst.

The methylene ketones, e.g.  $\text{CH}_3\cdot\text{CO}\cdot\text{C}\begin{smallmatrix} \text{CH}_3 \\ \diagup \\ \text{CH}_2 \end{smallmatrix}$ , are obtained by

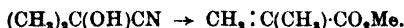
condensing an ethyl ketone with 40 per cent formaldehyde in alkaline solution and heating the resulting hydroxy compound with zinc chloride, when water is eliminated and the unsaturated ketone formed.



The chief commercial products are the polymerized styrene, methyl acrylate and methyl methacrylate; the latter,  $\text{CH}_2:\text{C}(\text{CH}_3)\cdot\text{CO}_2\text{CH}_3$ , readily polymerizes as a transparent

\* Morgan and others, C. and I., 1936, 319; 1937, 103. *Trans. Far.*, 1936, 1-412. Kienle, J. C. S. I., 1936, 229, T. *Polymerisation and its Applications*, New York, 1937. *High Polymers*, Vols. I and II, New York, 1941.

light-proof resin used under the name of *perspex* as a glass substitute. It is prepared by the action of methyl alcohol and sulphuric acid on acetone-cyanhydrin,



In the granular form obtained by polymerization of the emulsified ester the product is known as *diakon*, and is used in moulding processes. Both methylacrylonitrile,  $\text{CH}_2:\text{CMe}\cdot\text{CN}$ , and methylacrylamide,  $\text{CH}_2:\text{CMe}\cdot\text{CO}\cdot\text{NH}_2$ , are used for making polymeric plastics. The softer polymerized methyl acrylate is used in the textile industry for laminated glass layers, and the harder methyl homologue is also used for lacquers and moulding powders (cf. C. and I., 1938, 141).

Polystyrene is largely used in the electrical industry.

Many vinyl compounds polymerize spontaneously in light, some quickly, others slowly, but the process is accelerated by the addition of 0.1 per cent of a peroxide, e.g. benzoylperoxide, and to obtain products free from gas bubbles the process is often carried out in solution and subsequent removal of the solvent.

*Staudinger* gives the following types of synthetic high polymerides and the natural products which may be regarded as their analogues:

<i>Polymerized</i>		<i>Analogue</i>
1. Formaldehyde.	Insoluble.	Cellulose.
2. Styrene.	Homopolar colloids. Or- ganosols.	Caoutchouc.
3. Vinyl alcohol.	Mol. colloids with co-ordi- nate links. Hydrosols.	Starch.
4. Sodium acrylate.	Heteropolar mol. colloids. Hydrosols.	Cellulose xanthogenate and proteins.

They are all of the type



where X = H, Ph, OH or  $\text{C}\bar{\text{O}}\text{O}$ ,  $\text{Na}^+$ .

Various attempts have been made to establish relationship between structure and ease of polymerization, but so far only a few simple generalizations are possible. Ethylene and propylene polymerize only with difficulty, the unsymmetrical dimethyl- or dichloro-ethylenes or butadiene readily, and

phenylethylene (styrene) and acetylene,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}:\text{CH}_2$ , extremely readily. Generally symmetrically substituted olefines polymerize less readily than their unsymmetrical isomers. In the following conjugated compounds—butadiene, acrylaldehyde, acrylic acid and methylacrylate—the introduction of a methyl group  $\alpha$  to the olefine bond tends to inhibit polymerization, whereas a  $\beta$ -methyl group increases the tendency to polymerization.

Polymerization of unsaturated compounds can occur under different conditions:

(1) Spontaneously at moderate temperatures, e.g. formaldehyde, styrene.

(2) By light, e.g. vinyl chloride, bromide or acetate;

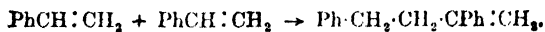
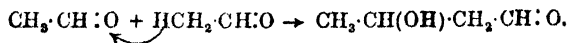
(3) By means of catalysts, e.g. Florida earth, certain halides, e.g.  $\text{BF}_3$ ,  $\text{SnCl}_4$ ,  $\text{AlCl}_3$ , and formic acid.

Compounds which polymerize only in the presence of a catalyst are isobutylene, anethole, indene.

The nature of the product, e.g. whether a dimeride, a trimeride, or a highly polymerized product, depends on the original substance and also on the conditions, e.g. styrene in the presence of a catalyst can yield a dimeride, whereas at moderate temperature without a catalyst highly polymerized products are slowly produced.

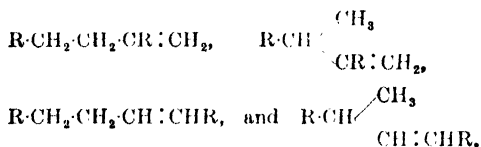
Two views are held as to the manner in which polymerization occurs:

(1) *The hydrogen separation hypothesis*.—Union is supposed to occur after the shifting of a hydrogen atom from one molecule to a second, e.g.

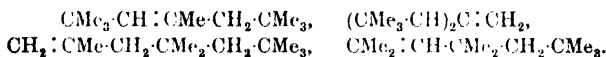


Most chemists are agreed that this type of reaction applies to the formation of simple forms, e.g. dimerides and trimerides, and *Whitby* holds that a similar step-wise addition occurs in the formation of the high polymerides. It will be noted that the polymeride contains the grouping which was characteristic of the monomeric form, e.g.  $\cdot\text{CH}:\text{O}$  in the first case and  $\cdot\text{CPh}:\text{CH}_2$  in the second. In the formation of a dimeride from

a monosubstituted olefine, theoretically it is possible for four distinct dimerides to be formed, viz.



and in the case of isobutene two dimerides have been isolated, and in the formation of triisobutene from isobutene and sulphuric acid the four trimerides have been isolated:



In support of his view that this type of reaction occurs in the formation of high polymerides, *Whitby* claims that it is possible to lengthen a polystyrene by the addition of a further molecule of styrene in the presence of a suitable catalyst, and also that the capacity for combining with bromine indicates the presence of olefine links in the high polymers.

(2) *Staudinger's long-chain formation*.—According to this the olefine link in the molecules of the monomer opens, and then head to tail union occurs: \* —CHPh·CH<sub>2</sub>[(CHPh·CH<sub>2</sub>)<sub>n</sub>CHPh·CH<sub>2</sub>—. This does not take place in definite slow stages but practically instantaneously, so that after even a short time no polymers of low mol. weight can be isolated. The chains so formed are of the general type given on p. 1073, and were originally represented with a free valency at each end. Subsequently *Staudinger* and *Steinhofer* suggested that there may be intermolecular migration of hydrogen and the formation of a terminal olefine link.

*Staudinger's* structure is supported by X-ray studies and also by the products formed on thermal decomposition, viz. styrene, 2:4-diphenyl-1-butene and 1:3-diphenylpropane.

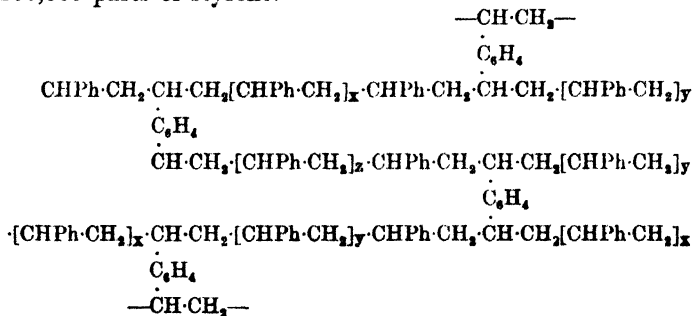
\* i.e. union occurs between the β-C atom of one molecule and the α-C atom of another. This does not occur in every case, as *Midgley*, *Henne*, and *Leicester* by hydrogenation of a styrene dimeride have obtained 1:4-diphenylbutane, CH<sub>3</sub>Ph·CH<sub>2</sub>·CH<sub>2</sub>·CH<sub>2</sub>Ph, indicating that union between the β-C atoms of the two molecules has taken place. The product —CHPh·CH<sub>2</sub>·CH<sub>2</sub>·CHPh—could polymerize further and the result would be a buckled chain, which might account for the electric properties of the polystyrenes (cf. *C. Ellis*, J. A. C. S., 1936, 1961).

The polymers have aromatic properties and can be nitrated, brominated, and hydrogenated without rupture of the molecule.

In the polymerization three distinct stages are recognized: (a) Formation of the nucleus from which the polymerization proceeds; (b) chain growth; (c) stabilizing reaction which causes the reaction to cease.

For *Staudinger's* classification according to length of chain, cf. *Trans. Far.*, 1936, 54, 296.

When styrene is polymerized rapidly with  $\text{SnCl}_4$  it gives a powdery polymeride belonging to group I, with an order of polymerization of 50–100; but when the polymerization proceeds slowly at low temperatures in the absence of a catalyst it gives a member of group II, viz. a eucolloid with thread-like molecules soluble in organic solvents and with a number 1000–5000. A mixture of styrene and *p*-divinylbenzene at 60°–100° gives a mixed polymeride in the form of a hard tough glass (group III), resembling the eucolloid from styrene itself, but insoluble even in large amounts of solvents, but swelling to a high degree. *Staudinger* regards this as a three-dimensional polymer formed by bridges of the divinylbenzene connected to the thread-like molecules of the polymeric styrene. The amount required is 1 part per 10,000–100,000 parts of styrene.



Possibly vulcanized rubber is a three-dimensional product formed by bridges of sulphur between the caoutchouc molecules.

Of all synthetic resins the polystyrenes have the highest electrical insulation properties; cf. also *Norrish* and *Brookman*, *P. R. S.*, 1937, 163 A., 205.

*Condensation polymerization.*—Similar to polymerization

proper--where the polymer has the same percentage composition as the monomer--is what is termed condensation polymerization, where large molecules are formed from a compound containing two or more reactive groups, e.g. OH, Cl,  $\text{CO}_2\text{H}$ ,  $\text{NH}_2$ , in the same molecule. In the reaction simple products are eliminated, e.g.  $\text{H}_2\text{O}$ ,  $\text{HCl}$ ,  $\text{NH}_3$ , and the polymer has a composition different from that of the monomer.

It is not necessary that all the molecules should be identical.

The reactivity of a compound is expressed by the number of reacting points in the molecules. The simplest type is with a reactivity 1. The reaction between two such molecules cannot result in the formation of long chains as the formation of the dimeride or double molecule exhausts the functions. Thus  $\text{CH}_3 + \cdot\text{CH}_3$  gives  $\text{C}_2\text{H}_6$ , but the reaction proceeds no further. Similarly an alcohol  $\text{R}\cdot\text{OH}$  and an acid  $\text{R}'\cdot\text{CO}_2\text{H}$  can condense to form an ester  $\text{R}\cdot\text{O}\cdot\text{CO}\cdot\text{R}'$ , but the process does not continue as the single function of each molecule is completely utilized.

With compounds containing an olefine linking, each molecule has two reactive points, viz. the points formed by the opening of one of the olefine links  $-\text{CH}_2\cdot\text{CH}_2-$ . By the union of two such molecules  $-\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2-$  a product is formed which still has two active points, and theoretically the process could continue indefinitely.

Other examples of the 2, 2 polymerization are:

(1) Formation of polyoxy-methylene chains from hydrated formaldehyde,  $\text{OH}\cdot\text{CH}_2\cdot\text{OH}$ ,  $\text{OH}\cdot\text{CH}_2\cdot[\text{O}\cdot\text{CH}_2]_n\cdot\text{OH}$ .

(2) Ester chain from a hydroxy-acid by intermolecular elimination of water. The two points are OH and  $\text{CO}_2\text{H}$ .

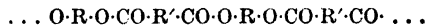


(3) Ester chain between molecules of a dibasic acid and of a glycol,  $n\text{CO}_2\text{H}\cdot\text{R}\cdot\text{CO}_2\text{H} + n\text{OH}\cdot\text{R}'\cdot\text{OH}$ , where R and R' are  $\text{CH}_2$  or polymethylene groups.

This latter reaction has been studied in detail by Carothers (1929-35), also polyamide formation and polyamide-polyester formation. Under reduced pressure  $\alpha$ -polymerides are formed with mol. weights of 800-5000, and readily soluble in suitable solvents. On prolonged heating under suitable conditions these forms pass into the  $\mu$ -forms or superpolyesters, with molecular weights of probably 20,000, and in physical properties closely resembling certain natural colloids in yielding



strong pliable highly orientated fibres, but unlike cellulose and rubber they are extremely sensitive to degradation by heat. Polyester from a glycol  $R(OH)_2$  and dibasic acid  $R'(CO_2H)_2$ :



Polyamide from  $NH_2 \cdot R \cdot CO_2H$ :



Polyester-polyamide from  $OH \cdot R \cdot CO_2H$  and  $NH_2 \cdot R' \cdot CO_2H$ :



In some cases not all the points function in the polymerization; they may function—owing to steric reasons—intramolecularly, and thus have nil reactivity as regards polymerization. Polymerization and condensation of the 2, 2 type leads to chain formation, except when cyclic compounds with 5, 6, or 7 numbers can be formed.

More complex are the polymerization or condensations of the 2, 3 type, i.e. one molecule with 2 reactive and the other with 3 reactive points. The simplest example of this is met with in the phenol formaldehyde condensation.

## 2. PHENOL-FORMALDEHYDE RESINS.\* NOVOLAC AND BAKELITE

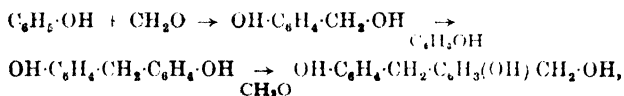
The reaction between formaldehyde and phenol is slow and requires an accelerator. When heated with a base the mixture undergoes condensation and separates into two layers, an aqueous layer which is of no value and a treacly mass which can be dried to form resin A, which is soluble in alcohol. This melts when heated but at the same time undergoes polymerization, and if heated under pressure forms the hard translucent resin known as *Bakelite*, which is used for making artificial jewellery, cigarette tubes, insulating materials in the electrical industry, and for numerous other purposes. The soluble resin A, or novolac type, is used for varnishes either with or without the addition of gum esters. The hard resin, bakelite, is usually made by the two-step process. The condensation to the novolac resin is accomplished with the aid of an acid accelerator and with excess of phenol, and further heating does not produce polymerization unless a base is

\* 1937, World production, 80,000 tons.

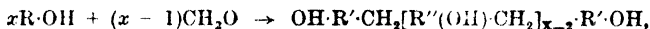
added together with excess of formaldehyde when the second step occurs and the hard resin is formed. Phenol itself is commonly used, but the cresols also give valuable resins and acetaldehyde behaves somewhat similarly to formaldehyde, and according to *Morgan* the phenols from low-temperature tars can also be utilized. It is noteworthy that the phenols used must be of a high degree of purity.

For the production of moulding powders the two-step process is always used, and before undergoing the second operation the novolac is mixed with a filler, usually very fine wood flour or cotton fibre and more formaldehyde or hexamethylenetetramine (p. 151), the mass being then moulded and heated in the mould.

Different views have been expressed on the structure of novolacs. *Baekland* and *Bender* favour the view that the first step is the formation of a phenoxy-hydroxy-methane,  $\text{PhO}\cdot\text{CH}_2\cdot\text{OH}$ , but *Megson* (*Trans. Far.*, 1936, 336; *J. S. C. I.*, 1939, 131) favours the view, which is the one usually accepted, that long chains are formed by the following reactions:



&c., and finally a long chain,

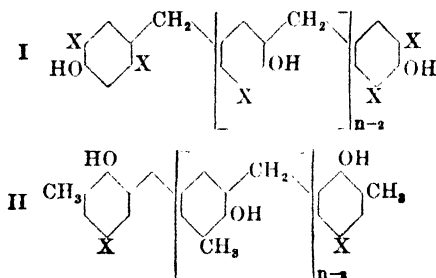


where R represents  $\text{C}_6\text{H}_5$ ,  $\text{R}' = \text{C}_6\text{H}_4$ , and  $\text{R}'' = \text{C}_6\text{H}_3$ , or analogous groups. They are regarded as linear polymers containing a mixture of compounds of different molecular weights. The introduction of  $\cdot\text{CH}_2\cdot$  group takes place in positions both *o* and *p* to the OH in the benzene rings, so that in the long-chain compound numerous isomers are possible.

Formaldehyde or its hydrate is a two-functional compound and phenol a three-functional, i.e. the two *ortho* and one *para* positions. In the formation of the long-chain molecules of the novolac type the latter acts only as a two-functional compound, as shown by only two of the nuclear hydrogen atoms being replaced. In the formation of bakelite by the action of excess of formaldehyde on the novolac, the third function of certain rings functions and the long chains of novolac become united by cross links of  $\cdot\text{CH}_2\cdot$ , not in a single plane, but in three

dimensions. This cross linking does not proceed in a regular systematic manner, as X-ray examination gives no indication of a crystalline scattering.

*m*-Cresol, like phenol, is three-functional, whereas *o*- and *p*-cresols are two-functional, hence the novolacs derived from the two types will differ. Those from the three-functional phenols can be represented by I, and those from the two-functional by II:



It is clear that I still contains a relatively large number of functional points denoted by X which can react with more formaldehyde or can take part in heat-hardening; type II contains relatively few functional points, viz. at the two ends of the complex molecule, and is therefore less reactive with formaldehyde or heat-hardening.

Extremely hard resins, formed from polyhydric phenols and formaldehyde with mineral acid as catalyst, when ground can remove either cations or anions from aqueous solutions of salts (*Morgan*, C. and I., 1937, 111) and hence can be used as water softeners.

Phenolic plastics can be utilized as extruded materials, e.g. rollers, beadings, handles, &c.

Products termed **semisynthetic plastics** are obtained by condensing lignins (p. 368) with phenols (e.g. cresols), amines (e.g. aniline), aldehydes (e.g. furfural), and a catalyst, and are extremely cheap to manufacture. Another type is made by condensing formaldehyde with tannins.

The resins obtained from individual phenols vary remarkably in character. The most valuable are those derived from phenol, 1:3:5-xyleneol and resorcinol. *o*- and *p*-Cresol tend to give crystalline products, and it appears that the greater

the number of isomerides possible, e.g. phenol and *m*-cresol, the greater the value of the resin.

The moulding powders can be used for the same purposes as cellulose acetate moulding powders, e.g. for telephones, cabinets, boxes, ash trays, switch plugs, wall plates, &c. The resins are also largely used for the manufacture of laminated products, e.g. boards made from paper, fabric or asbestos impregnated with novolac and hardened under heat and pressure. The products are used in the electrical industry and for doors, wall panels, &c.

Resins soluble in linseed oil and therefore of value in the paint and varnish industry can be made by condensing certain homologues of phenol with formaldehyde. Of these phenols the more important are the 1 : 5, 3 : 4, 1 : 4, and 3 : 5-methylphenols, *p*-*tert*-butylphenol, *p*-*tert*-amylphenol, *p*-dihydroxydiphenyl, and  $p\text{-OH}\cdot\text{C}_6\text{H}_4\cdot\text{CMe}_2\cdot\text{C}_6\text{H}_4\cdot\text{OH}$ . In the majority of these one ortho or more generally the *p*-position in the phenol, is substituted, so that the compound is only two-functional as regards formaldehyde and thus gives chains of the novolac type.

Some of these appear to be of comparatively low molecular weight (C. I., 1938, 8).

The compounds with branched alkyl groups, e.g. *tert*-butyl and *amyl* are of great value. The resins are often termed **alkyd resins**.

### 3. UREA PLASTICS OR AMINOPLASTICS \*

Commercial formaldehyde and urea with or without the addition of thiourea yield a hard resin which has been utilized for making unbreakable cups and laminated sheets for decorative panelling; also as a filler for textiles and as a component of lacquer finishers. The usual method is to obtain a syrup by the action of formaldehyde solution, using as little as possible, on a mixture of urea with not more than 50 per cent of thiourea. The syrup, containing 50–60 per cent of resin, is mixed with fine wood pulp and masticated. After drying and grinding this gives a moulding powder. The moulds are made of stainless steel. If thiourea is not used the resin formed is not so resistant to the action of water.

According to *Walter* (Trans. Far., 1936, 377), the primary

\* C. and I., 1935, 102; 1937, 639.



chanically it is not so strong as other synthetic resins and is strictly non-thermoplastic.

## 6. CELLULOSE ESTER AND ETHER PLASTICS \*

The use of celluloid nitrates in the form of collodion has been described in Chap. XIV, C., and they still form some of the commonest plastics.

Certain esters and ethers of cellulose, unlike the parent compound, are thermoplastic, i.e. they become softer when heated and hence can be moulded and harden again on cooling. The operation can be repeated a number of times without the property being destroyed.

As materials for moulding powders and injection moulding cellulose acetate and benzylcellulose are most frequently used and are mixed with gelatinizers, pigments and fillers. The acetate has replaced the nitrate for safety-glass manufacture and for non-inflammable films. For cellulose lacquers used for spraying the usual basis is nitrocellulose, less generally acetyl and benzyl celluloses, with a gum or ester gum, a plasticizer, e.g. tricresyl phosphate and solvents, the most important of which are alcohol, toluene, ethyl acetate, butyl alcohol and butyl acetate, and a suitable pigment. *Cyclohexanone* is an excellent solvent but has an objectionable odour. The monomethyl and monoethyl ethers of glycerol and glycol are good solvents. A common one is *cellosolve*, the monoethyl ether of glycol. It is not advisable to use a solvent with too low a boiling-point, as rapid evaporation lowers the temperature and moisture is deposited on the film.

Benzyl cellulose is used for thin wrapping material and for book cloths, as it is highly water resistant.

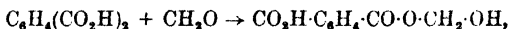
For plastic purposes cellulose esters cannot be used alone; they require the addition of a plasticizer, i.e. a substance which will give the material greater extensibility and at the same time render it less rigid or softer. Resins and ester gums are often used. Type (a) has no solvent action on the ester, and gives an opaque mixture which requires a second plasticizer or a solvent to yield a more plastic transparent product. Type (b) is rare, and consists of resins which act as solvents for the ester and give directly a transparent product.

\* C. and I., 1933, 705; 1937, 591. *Technology of Cellulose Ethers*, Woden, New York, 1933.

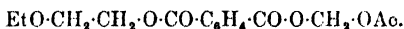
Probably certain plasticizers form additive compounds with cellulose nitrate. The plasticizer has a great influence on the gloss of a film and on the flowing properties of a cellulose ester solution. Among synthetic plasticizers are triacetin, tributyl and tricresyl phosphates, triethyl and tributyl citrates, dibutyl tartrate, diethyl phthalates, butyl, dibutyl and diamyl benzyl, and *cyclohexyl* laevulinate, and certain sulphonamides.

Tricresyl phosphate is a favourite, as it does not destroy the elasticity of the non-plasticized film as much as most others. Camphor has the same effect but is more volatile. Castor oil is also used, but it is merely a diluent not a solvent.

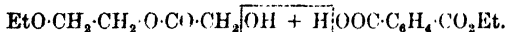
Other types are the methylene glycol esters obtained from dibasic acids like phthalic acid and formaldehyde:



the product having both a free OH and a free  $\text{CO}_2\text{H}$  group, and can react with cellosolve and acetic acid, yielding



Numerous complex compounds of a similar type are also used, e.g. the product formed by esterifying an acid ester of phthalic acid with the ester of a hydroxy acid, e.g. cellosolve glycolate:



Also compounds di- $\beta$ -phenoxyethyl phthalate,  $\text{C}_6\text{H}_4(\text{CO}\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OPh})_2$ , and butylene-glycol phthalates.

## LXI. THE CHEMISTRY OF RUBBER \*

In the domain of organic chemistry few subjects afford a better illustration of the interplay of scientific, technical, and commercial factors in the development of an industry than rubber does.

The importance of the rubber industry can be gathered from the fact that even in 1911 it represented an annual value of about £45,000,000, or roughly twice the value of the

\* Cf. *Fischer, Chem. Rev.*, 1930, 51.

synthetic dyestuffs industry. The production for that year was about 100,000 tons, and this increased by 1934 to 1 million tons and has fluctuated round that figure for the past few years. The price has varied within wide limits, viz. 4s. per pound in 1923 to 3d. per pound in 1933, and depends upon supplies and demand. The motor-tyre industry increased the demand and raised the price, but the very rapid development of new rubber plantations in the East increased the supply and reduced the price.

Rubber is manufactured from the milky-white, sticky juice or latex produced when certain species of trees, shrubs, and creepers are tapped or cut.

The three stages in the production of commercial rubber are:

- (1) The collection of the latex; (2) the coagulation of the latex, and the production of raw rubber or caoutchouc; and (3) the curing or vulcanization of the raw rubber.

## A. Sources of Rubber. The Latex. Coagulation

*Sources of Rubber.*—The chief rubber-producing countries are: South America, notably the regions of the Amazon and Para, East and West Africa, the Malabar Coast of South India, Burma, Ceylon, the Malay Peninsula, Siam, and Cochin China. In South America the latex is obtained from species of *Hevea*, more particularly *H. Sileri* and *H. brasiliensis*, a good specimen of which will yield as much as 22 lb. of rubber per annum. The trees are all of wild growth, the cost of collection high, and the coagulation methods crude. The product "Para Rubber" comprises only 10–15 per cent of the total rubber supplies.

Small amounts are also obtained from certain tropical African creepers, and also from other rubber trees, e.g. *Casilloa costaricana* in Mexico.

Roughly, 80–90 per cent of the world's supplies of dry rubber are derived from the rubber plantations in Asia.

Extensive plantations were laid down by the British in 1876 in Ceylon and the Federated Malay States, by the Dutch in 1882 in Java, Sumatra, Borneo, and in 1885 by the French in Tonkin, Cambodia, and Laos. The majority of the plantations consist of *Hevea*, which are propagated by seeds, or more



frequently by cuttings. The trees begin to yield rubber in workable quantities when six to ten years old; at first they are tapped every other year, but when mature can be tapped every year, usually after the rainy season, and never during the period of flowering. The yield of rubber from a mature tree is about 3.5 to 4.5 lb. per annum. The best estates yield as much as 1200 lb. per acre, but the average is only 400 lb.

The enormous increase in the production of plantation rubber is largely due to the scientific management, the relatively low costs of production, and the better transport facilities as compared with South America.

*The Latex.*—The latex of *Hevea* is a white sticky liquid with the consistency of cows' milk, and the specific gravity varies with the amount of rubber it contains. It is an emulsion of rubber in water which holds in suspension or solution glucosides, sugars, resins, proteins, enzymes, organic acids, and mineral salts. The composition varies within wide limits according to the botanical source, the age of the plant, the season, the method of production, and the height above ground at which tapping occurs. The percentage of rubber tends to increase with the age of the tree (as a rule trees should not be tapped until they are 6–10 years old), and to diminish with the height of the tap hole from the ground.

The following may be taken as typical analyses of *Hevea* latex:

		Amazon Delta		Ceylon Plantation
Water	..	.. 47.0	..	.. 55.2
Rubber	..	.. 32.0	..	.. 41.3
Mineral salts	..	.. 9.7	..	.. 0.4
Proteins	..	.. 2.3	..	.. 2.2
Resins	..	.. 9.0	..	.. 2.0
Sugars	..	.. —	..	.. 0.4

Nearly all latices contain small amounts of sugars and glycosides. Most of the sugars appear to be related to inositol (p. 487), and not to the glucose group. The substance known as **Dambonite**,  $C_6H_{16}O_6$ , and present in most latices, appears to be an inositol dimethyl ether,  $C_6H_6(OH)_4(OCH_3)_2$ . *l*-Inositol monomethyl ether is also present in *Hevea* latex.

Most latices are alkaline to litmus when freshly tapped, but when kept they undergo bacterial fermentation producing organic acids, mainly lactic, which bring about coagulation. The latices from species of *Ficus* are acid. Oxidases are usually

present, and when exposed to the air the latex tends to turn brown. The addition of a little sodium bisulphite prevents this darkening without impairing the properties of the rubber. Anti-oxidants, probably unsaturated sterols, are also present (Ind. Eng. Chem., 1927, 1187).

The functions of the latex in the plant are: (1) a reservoir of nutritive material and water; (2) a medium for transportation of materials necessary for growth; (3) a protective material produced by the plant to assist in healing wounds, and to protect the plant against insect attacks.

**Use of Rubber Latex.\***—There is a growing tendency to export the latex or concentrated latex, and the amount has risen from 10,000 tons (calculated as dry rubber) to 30,000 tons in 1939. The latex has the advantage over dry rubber that the rubber can be vulcanized at lower temperatures, and the material contains the natural anti-oxidants present in the latex, so that the vulcanized product keeps better and also has greater mechanical strength than the masticated product. Fillers and accelerators can also be mixed in the moist state and vulcanization carried out at temperatures below 100°. The latex is used where the processes known as spreading, spraying, dipping, flocculation, moulding and electrophoresis are required; and articles made from latex are gloves, paper size, thin coatings for preserving metals, spongy material, impregnating fabrics to form rubber boots, and other products which cannot readily be manufactured from ordinary dry rubber.

For purposes of transit the latex must be protected against coagulation, usually by the addition of ammonia or an amine, and to avoid excessive transport costs is usually concentrated (J. S. C. I., 1937, 397 T.) by (a) centrifuging; (b) keeping and removing the cream; (c) evaporating under reduced pressure in presence of a stabilizer, e.g. potassium fluoride or silicate; (d) creaming by addition of Iceland moss or gelatine. Such creams contain about 75 per cent of rubber hydrocarbon and are mainly free from the water soluble non-rubber constituents of the latex, but contain the creaming agent. They can easily be diluted with water.

In the electrodeposition of rubber the particles are negatively charged and are deposited on the anode. In order to

\* *Rubber Latex*, Rubber Growers' Association, 1933. *Latex in Industry*, R. J. Noble, New York, 1936.

avoid loss of current it is necessary to remove strong electrolytes before deposition, and hence it is advisable to use ammonia rather than potash as a preservative, and to concentrate by centrifuging rather than by evaporation under reduced pressure.

It is necessary before electrodeposition on a metal surface to provide a bonding material between the metal and rubber; a modified rubber material "Vulcabond" is used for this purpose. An artificial latex can be made by incorporating dry rubber or reclaimed rubber with water and suitable coagulants, but such a latex is inferior to the natural product as the milling processes used in producing the dry rubber lessen its mechanical strength.

**Coagulation.**—Three methods of coagulation are used, viz.:

1. The smoking process adopted in the Amazonian district consists partly in the coagulation of the rubber by the rapid evaporation of the serum as it is exposed in a thin layer to hot smoke, partly in the coagulation by the acids present in the smoke, viz. carbonic, formic, and acetic, and preservation of the rubber from decomposition by the creosote contained in the tar.

2. *The Acid Process.*—The great bulk of the plantation latex is usually coagulated by acetic acid. Other acids or acidic substances can also be used, for example, formic, lactic, sulphuric acids, sodium hydrogen sulphate, alum, sulphurous acid, &c. This process of coagulation necessitates careful washing of the raw rubber in order to remove the acid. The quantity of acetic acid used is usually 1-2 per cent of glacial acid calculated on the latex, but can be varied within fairly wide limits. The addition of too much is harmful, as the rubber obtained does not cure so readily. In actual practice the amount of acetic acid added for coagulation is usually insufficient to produce coagulation by itself, and the view generally held is that the coagulation is due to an enzyme which is activated by the addition of acid, and that the process is somewhat analogous to the setting of milk by rennet (*Barrowcliff*, J. S. C. I., 1918, 48 T.).

The addition of a large amount of acid destroys the enzyme, and the coagulation is then due to the action of the acid on the negative suspensoid.

3. *Auto-coagulation.*—When the latex is mixed with about 0.2 per cent of glucose and kept, coagulation due to non-

putrefactive bacterial action occurs, and is complete in eighteen hours. The coagulum has a sweet odour, whereas in the absence of glucose putrefactive bacteria tend to develop, and the coagulum acquires a nauseous odour. If air is excluded the coagulation is not complete. This method is used in the Malay Peninsula, and may in time replace the acid process.

The latex is regarded as a milky fluid containing minute globules of a colloid, probably rubber itself, in a state of colloidal suspension in an aqueous fluid. In Hevea latex the globules are microscopic and show Brownian movements. It is a negative suspensoid and behaves as such; acids produce coagulation or precipitation, and alkalis increase the stability of the suspension. The protein content of the latex increases the stability of the suspensoid, the dissolved protein or peptone acting as a protective colloid.

If the latex is freed from saline matter by dialysis through a collodion film, salts of univalent metals have practically no effect, salts of bivalent metals produce coagulation at any concentration above normal, and salts of trivalent metals at concentration greater than 0.05 N. Acids produce the same effect at concentration of 0.5 N (*V. Henri, C. R., 1907, 144, 431*).

## B. Raw Rubber

The clots formed during coagulation consist of separate particles united to form a tenacious elastic network, and the structure of the clot varies with the coagulant used. Weak coagulants produce a network with an open mesh and slight elasticity, whereas strong coagulants produce a close mesh and a clot of high elasticity.

Like most gels, rubber itself is an emulsoid consisting of the colloid hydrocarbon rubber  $(C_{10}H_{16})_n$  in a fine state of dispersion in a colloidal medium, consisting partly of protein, but mainly of a modification of rubber. Thus rubber not only forms the disperse phase, but also its own dispersion medium.

During the process of coagulation a portion of the resins, proteins, and mineral salts are precipitated with the rubber. Para rubber contains much larger quantities of these impurities than plantation, and the presence of some of the nitrogenous substances is advantageous as it facilitates the subsequent process of curing.

Most of these impurities can be removed by dissolving the rubber in a suitable solvent. As in the case of most gels, the solution is preceded by a process of swelling or adsorption of solvent, and, finally, a colloidal solution of high viscosity is obtained which is difficult to filter. Benzene can be used in this way, and if a little trichloroacetic acid is added subsequently the solution becomes limpid, and can be easily separated from the impurities. Carbon disulphide, benzene, and chloroform yield almost transparent clear solutions, whereas ether and petroleum ether yield turbid liquids. The turbidity is due to the fact that the rubber is not so soluble in these solvents, and the insoluble part exists in a finely dispersed form throughout the solution. Even the apparently clear benzene solutions exhibit discontinuity under the ultra-microscope.

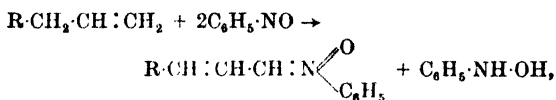
The impurities, e.g. resins and proteins, present in the raw rubber are not removed in practice, as the expense would be great, and as it has been found that the resins tend to prevent the oxidation of the rubber, and the proteins accelerate the process of vulcanization.

The soluble portion consists of a hydrocarbon  $(C_{10}H_{16})_n$ , but usually contains combined oxygen, e.g. 0.61 per cent in Para.

The following are the most characteristic rubber derivatives. A **tetrabromide**,  $C_{10}H_{16}Br_4$  (*Gladstone and Hibbert, Weber*), which has no definite melting-point but decomposes when heated. An **iodide**,  $C_{10}H_{16}I_3$  (*Weber*), in the form of a brown powder decomposed by light or heat. A **dihydrochloride**,  $C_{10}H_{18}Cl_2$ . A **monohydriodide**,  $C_{10}H_{17}I$  (*B.*, 1913, 1283). The product obtained by the removal of halogen hydracids from these compounds by means of bases is not identical with the original rubber, and is termed  $\alpha$ -iso-caoutchouc (*B.*, 1913, 736). A **nitrosite**,  $(C_{10}H_{16}N_2O_3)_n$  (*Harries, B.*, 1900, 779), obtained by passing dry nitrous anhydride fumes into a benzene solution of pure rubber, is a friable, greenish solid, insoluble in most solvents, and has no definite melting-point. A **nitrosite**,  $C_{30}H_{30}O_{14}N_6$ , obtained by passing moist nitrous gases into a benzene solution of rubber; it decomposes at  $158^{\circ}$ – $162^{\circ}$ , and is used in estimating rubber. An **ozonide**,  $C_{10}H_{16}O_6$ , obtained by passing purified ozonized air into a 1 per cent chloroform solution of rubber (*Harries, B.*, 1904, 2708; 1912, 936), evaporating to dryness at  $20^{\circ}$ , dissolving in ethyl acetate, and precipitating with petroleum ether. It

forms an explosive vitreous mass, melting at  $50^{\circ}$ , and is soluble in most solvents.

The rubber molecule also reacts with nitrosobenzene in much the same manner as olefines do, yielding a **nitrone**, e.g.



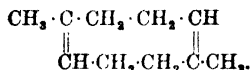
accompanied by a shifting of the olefine linking.

The empirical formula deduced from analysis is  $\text{C}_5\text{H}_8$ , and the formation of the derivatives already described indicates that the simplest formula is  $\text{C}_{10}\text{H}_{16}$  with two olefine linkings in the molecule, as the smallest molecular weight for the ozonide, determined by the cryoscopic and ebulliscopic methods, is 230. The general properties indicate a much more complex molecule, but as the molecular weight cannot be determined, the value of  $n$  in the formula  $(\text{C}_{10}\text{H}_{16})_n$  is uncertain, but is usually accepted at 6-8. At temperatures up to  $180^{\circ}$  the complex  $\text{C}_{10}\text{H}_{16}$  is still retained, although the ordinary physical characteristics have altered. At higher temperatures decomposition products are formed, and oily products equal in weight to 84 per cent of the rubber used are obtained. This distillate dissolves raw rubber at the ordinary temperature, and contains butylene, isoprene, a terpene hydrocarbon, dipentene, and a sesquiterpene, **hevene**, boiling at  $255^{\circ}$ - $265^{\circ}$  (*G. Williams*, 1860, and *G. Bouchardat*, *Bull.*, 1875, **24**, 108.)

**Constitution of Rubber.**—The constitution is largely based upon the following considerations: (a) the close relationship between isoprene and rubber; (b) the formation of the additive compounds mentioned above; and (c) a study of the decomposition products of the ozonide.

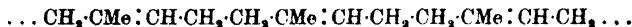
*Tilden* (*Chem. News*, 1882, **46**, 220), who prepared isoprene by breaking down pinene and dipentene, was the first to suggest the constitution of isoprene as 2-methyl- $\Delta^{1:3}$ -butadiene (p. 952), a conclusion which has since been confirmed by various syntheses. As isoprene yields rubber under the influence of heat or of small amounts of various chemicals, the latter would appear to be a polymer of isoprene. Its reactions with bromine, hydrogen chloride, nitrogen peroxide, and ozone indicate the presence of two olefine linkings in each  $\text{C}_{10}\text{H}_{16}$  portion of the molecule. When the ozonide is decomposed

by boiling water the products are lævulic aldehyde,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHO}$ , and lævulic aldehyde peroxide, which yields lævulic acid (p. 264), and hydrogen peroxide, and to account for these products *Harries* suggested the cyclic structure, viz. a polymer of 2 : 6-dimethyl-cyclo-octadiene:

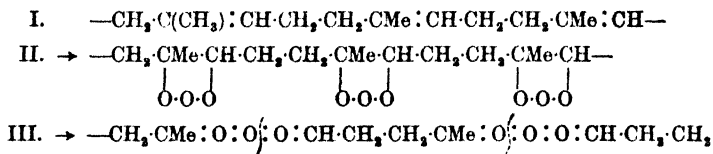


This view is not generally accepted.

*Weber, Pickles* (J. C. S., 1910, 1088), and others consider the rubber complex is a long chain built up from  $\text{C}_5\text{H}_8$  groups by normal polymerization, and with the two ends joined to form a closed ring, e.g.



The number of the  $\text{C}_5\text{H}_8$  groups is uncertain, and *Staudinger* considers it may be as high as 2000 units forming an *open* chain. In this polymerization a shifting of olefine linkings has taken place, and the formation and decomposition of the ozonide can be accounted for as follows: A molecule of ozone is added on at each olefine linking



The union between the carbon atoms is then ruptured, so that the ozonide has the structure No. III, which is decomposed by water into lævulic aldehyde and the corresponding peroxide as indicated by dotted lines (cf. *Ostromisslenski*, J. Russ., 1915, 1932.)

In the open-chain structure the olefine linkings allow of *cis* and *trans* isomerides, and X-ray examination of rubber indicates that the H and  $\text{CH}_3$  of the  $\cdot\text{CH}:\text{CMe}\cdot$  groups are all *cis*, whereas in caoutchouc they are *trans* (*K. M. Meyer*, C. and I., 1938, 439).

When heated alone, or with sulphuric acid or organic sulphonyl chlorides, rubber yields isomers which are less satu-





perature (e.g. steam under 50 lb. pressure); or in the Netherlands Government Institute 7.5 and 92.5 per cent respectively for 1.5 hours, with steam at 52 lb. pressure. The mechanical properties of the samples are determined, and the period of vulcanization necessary to produce optimum mechanical properties ascertained from the results of the tests.

The coefficient of vulcanization =  $\frac{\text{combined sulphur} \times 100}{\text{rubber}}$ ,

the name combined sulphur denoting the sulphur which cannot be extracted by acetone. According to *Spence*, at optimum cure this value is about 2.8-3, but other authorities give the value 4-5 for rubbers which have the greatest tensile strength.

Vulcanization consists in a small percentage of sulphur combining with the rubber molecules and a further amount being absorbed. In all probability the combined sulphur forms bridges between chains of rubber molecules forming molecules of 3 dimensions in the same manner as with polymerized olefine plastics (Chap. LX, C1).

Selenium (1926) can also bring about vulcanization, and mixed with sulphur gives excellent results. Small amounts of rubber hydrochloride bring about vulcanization, and certain polynitro-benzenes behave in the same way (*Ostromisslenski*).

The substance known as vulcanite (cf. p. 1093) or ebonite is manufactured by heating raw rubber with larger quantities of sulphur (65 : 35) for a longer time at higher temperatures. The physical properties characteristic of the rubber are thus completely changed, and a brittle product, probably consisting of compounds  $(C_5H_8S)_x$ , is formed.

Many rubber goods do not consist simply of vulcanized caoutchouc, but contain fillers. These are added partly to reduce the cost of the rubber and partly to modify its properties for particular purposes; thus mineral matter, such as zinc oxide or magnesia, is usually added when the rubber is required for mechanical purposes involving abrasion and compression; on the other hand, if a colourless eraser is required, a large amount of "white rubber substitute" is added. This substitute is prepared by the action of sulphur monochloride on rape oil. Various materials are also used as pigments. Antimony sulphide is the commonest, and others are yellow sulphide of arsenic, oxide of chromium, zinc chromate, ultramarine, and lamp black. Glue is also used as a filler.

Reclaimed rubber and bitumen are also used for mixing

with the rubber. The reclaimed rubber is obtained by reducing old rubber or waste rubber to a fine state of division, treating with acid or alkali, washing with water, and subsequently steaming under pressure in order to render it plastic. Reclaimed rubber, like vulcanized rubber, is insoluble in solvents which dissolve raw rubber; the process of reclaiming does not remove the combined sulphur and frequently only a portion of the fillers present in the waste.

**Accelerators** (C. and I., 1933, 90, 95).—Milled plantation rubbers and synthetic rubbers are much more difficult to vulcanize than latex or Para rubber. This is due to the absence of basic accelerators in the former. During the process of washing the coagulum to remove acetic acid much of the protein matter is removed. This deficiency is rectified by the addition of suitable **accelerators**, and *Eaton and Grantham* (J. S. C. I., 1915, 989; 1916, 715) have shown that a rapidly curing rubber of good mechanical properties is obtained if the slabs of wet coagulum are allowed to stand for 6–10 days before further treatment. This is probably due to the liberation of basic nitrogenous compounds by enzymes from proteins left in the coagulum, and subsequent washing and heating in a dryer does not completely remove these compounds.

For ordinary raw rubber it is necessary to add an accelerator before vulcanization. Two common accelerators used for a number of years were aniline and thiocarbanilide,  $\text{CS}(\text{NHPh})_2$ , also metallic oxides, e.g. magnesia, lime and litharge. Other organic bases, e.g. piperidine, diamines, aldehyde-ammonia, and numerous other bases with dissociation constants greater than  $1 \times 10^{-9}$ . If the bases are too volatile they are used in the form of their carbamates, carbonates or carbamides. Hexamethylenetetramine (p. 151) and guanidines, e.g. diphenylguanidine, are also used. The thiocarbanilides are extremely reactive.

The addition of an accelerator not only shortens the time or lowers the temperature required for vulcanization, but also improves the properties of the vulcanized product in several respects, e.g. tensile strength, resistance to abrasion, and tends to lengthen the life of the material.

**Delayed Accelerators** (*Twiss and Jones*, J. C. S. I., 1935, 13 T.).—Some accelerators work too rapidly and produce what is termed "scorching" during the processing operations preliminary to vulcanization. This has led to the use of

delayed action accelerators. A common practice is to introduce into the accelerator molecule a group which will lessen its accelerating properties, but which is subsequently removed, thus setting free the full activity of the accelerator. Most accelerators contain an active hydrogen atom, and in the delayed accelerator this is replaced by a displaceable organic radical, which by subsequent hydrolysis or fission is removed, thus liberating the accelerator.

Accelerators which require restraining are of the dithio acid and mercaptobenzthiazole types. Examples of the former are:

Alkyl xanthates,

Dithiocarbamates,

derived from secondary amines including piperidine, and of the latter:

1-Mercaptobenzthiazole,  $\text{HS}-\text{C} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{S} \end{array} \text{C}_6\text{H}_4$ , and its substituted derivatives, which are some of the commonest accelerators;

Benzthiazyl sulphides,

and the delayed accelerators are the aryl esters of the dithio acids and also esters of the thiazoles with organic acids.

Examples are:

I.  $\text{S}:\text{C} \begin{array}{c} \diagup \text{S}-\text{C}_6\text{H}_3(\text{NO}_2)_2 \\ \diagdown \text{NC}_5\text{H}_{10} \end{array}$  2:4-dinitrophenyl-piperidine carbothionolate;

II.  $\text{S}:\text{C} \begin{array}{c} \diagup \text{SC}_6\text{H}_3(\text{NO}_2)_2 \\ \diagdown \text{NR}_2 \end{array}$  2:4-dinitrophenyl-dialkyldithiocarbamates,

which hydrolyse to  $\text{S}:\text{C} \begin{array}{c} \diagup \text{SH} \\ \diagdown \text{NC}_5\text{H}_{10} \end{array}$  and  $\text{S}:\text{C} \begin{array}{c} \diagup \text{SH} \\ \diagdown \text{NR}_2 \end{array}$ .

III. 1-Benzthiazyl thiostearate or benzoate,  $\text{R}\cdot\text{CO}\cdot\text{S}-\text{C} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{S} \end{array} \text{C}_6\text{H}_4$ ;

IV. 2:4-dinitrophenyl-benzthiazyl sulphide,  $(\text{NO}_2)_2\text{C}_6\text{H}_3\cdot\text{S}-\text{C} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{S} \end{array} \text{C}_6\text{H}_4$ ,

but numberless compounds have been patented.

Mixed accelerators are often employed, e.g. No. IV with diphenylguanidine.

Another method of preventing scorching is by adding a second compound which will retard the activity of the accelerator without apparently reacting with it. Such compounds are termed "antiscorch reagents". They comprise certain resins and acids of the fatty series or their aniline or urea salts.

**Antioxidants.**—Ordinary rubber goods on exposure to light and air undergo "ageing", a process of oxidation which renders the products hard, brittle, and liable to crack. Chemical substances, in very small amounts, are introduced in order to diminish this oxidation. These can be applied in solution to the rubber surface, but are usually incorporated in the mix. Phenols and hydroxylic compounds, amines, condensed amines and aldehydes, e.g. two bases condensed with one aldehyde, and numerous other compounds have been suggested. Some have the disadvantage that they affect the colour of the rubber and others produce "bloom".

## D. Rubber Derivatives

Certain rubber derivatives have found use in the plastics industry. One of these is a rubber-tri-halide used as a thin wrapping material and weight for weight 20 per cent greater area than usual cellulose ester materials. Another is chlorinated rubber prepared by chlorinating rubber solutions, and finds use as a lacquer for electrical insulating purposes and is practically non-inflammable and resistant to acid and alkali. It contains some 65 per cent of chlorine, and may be represented at  $(C_6H_6Cl_4)_n$ . Sulphonated rubber compounds and derivatives obtained by oxidizing rubber with oxygen in presence of catalysts or with hydrogen peroxide in acetic acid solution, e.g.  $C_{10}H_{16}O$ , are used in the manufacture of paints, &c.

## E. Synthetic Rubbers

The term synthetic rubber is given not merely to a product which is identical, so far as can be determined, with the natural product, but also to substances with rubber-like qualities and

closely related structures but certainly not identical. A synthetic product from isoprene need not necessarily be identical with natural rubber; in the one case the compound may be  $(C_5H_8)_n$ , and in the other  $(C_5H_8)_m$ , and even with a formula  $(C_5H_8)_n$  there may be two compounds with the same formula but with the olefine links in different positions. Products like the Russian synthetic rubber and the American product, duprene, are obviously quite different in composition from natural rubber.

Numerous methods of preparing isoprene and analogous conjugated dienes have been worked out (for summary, cf. *Ostromisslenski*, J. Russ., 1915, 1472; Abs., 1916, i, 2), and numerous methods of bringing about the polymerization, but at the present time only three synthetic products are being manufactured on a comparatively large scale.

These are the German and Russian hydrocarbons and the chlorinated product duprene or neoprene. It is not claimed that these compounds can be made at a price which can compete in the open market with natural rubber at 4*d.* or even 8*d.* per pound. The two hydrocarbons are being manufactured because the countries involved have an insufficiency of foreign exchange to pay for imported rubber, and also because they wish to have their own sources for rubber in case of war. Duprene and German synthetic are also manufactured because, for certain specific purposes, they are superior to natural rubber.

1. *German Synthetic Rubber*.—During the Great War Germany manufactured an appreciable amount of methyl-rubber—a polymer of 2:3-dimethylbutadiene—but the chief source is now the simple butadiene manufactured from calcium carbide as starting-point. The products are termed **Buna** 1, 2, &c., and appear to have different values of  $n$  in the formulæ  $(C_4H_6)_n$ , as indicated by the different viscosities of solutions. When reinforced by the addition of gas black as a filler they form valuable products, and even without a filler they yield excellent ebonites. The curing is similar to that of natural rubber, i.e. with sulphur, zinc oxide, an accelerator and an antioxidant.

Another important series of synthetic products is made by polymerizing butadiene with some 10–30 per cent of another polymerizable substance, usually styrene or acetonitrile. The products—the so-called interpolymers—are met with under

the names **Buna S** and **Buna N**. The production in 1938 was 24,000 tons. These products are harder and tougher than natural rubber and respond less readily to heat, and in all probability they have a crossed chain structure—analogueous to S vulcanized rubber but with a carbon linking in place of sulphur. They do not mill well, and take large quantities of fillers (softeners) without losing tensile strength. They are often used in admixture with natural rubber. They are less affected by oils than natural rubber and have higher resistance to abrasion (30 per cent). For the production of butadiene, aldol is manufactured from acetylene by the stages mentioned in Chap. LI, F. The aldol is reduced electrolytically or by neutral reducing agents to 1:3-butylene glycol,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , which on catalytic dehydration yields butadiene,  $\text{CH}_2\text{:CH}\cdot\text{CH}\text{:CH}_2$ .

The polymerization is effected by means of metallic sodium (0.5 per cent of the butadiene) deposited on an iron comb, and proceeds in autoclaves under pressure and careful temperature regulation.

2. *Russian Synthetic Rubber*, SKB (cf. *Rubber Age*, 1935, 16, 14).—The basis of this process is divinyl (butadiene),  $\text{CH}_2\text{:CH}\cdot\text{CH}\text{:CH}_2$ , formed by the "cracking" of superheated alcohol vapour with a mixture of aluminium and zinc oxides. The reaction involves the removal of water and hydrogen (dehydration and dehydrogenation).

Probably the alcohol by dehydrogenation yields acetaldehyde which reacts with alcohol, yielding water and butadiene. The latter is carried over with the gaseous products, and is extracted by scrubbing, using petroleum, and subsequent distillation. Various by-products are formed, including acetaldehyde, ethyl ether, and butyl alcohol. The polymerization is brought about by the use of sodium (0.5 per cent).

It is claimed that 100 parts of alcohol give 23.1 parts of rubber, and in 1935 about 25,000 tons were manufactured, and a certain amount of ether recovered as a by-product. The polymerization is exothermic and is carried out in autoclaves at 8 atm. pressure and 65° during 90–120 hours, and finally at 40° for 3–8 days. The product is worked up in much the same manner as raw rubber, and requires fillers, accelerators and antioxidants, e.g. 0.5 to 1.0 per cent of aldol- $\alpha$ -naphthylamine, before vulcanization. In 1936 about half Russia's demands for rubber were met by this synthetic product.

For the part taken by the sodium during polymerization, cf. Trans. Far., 1936, 295.

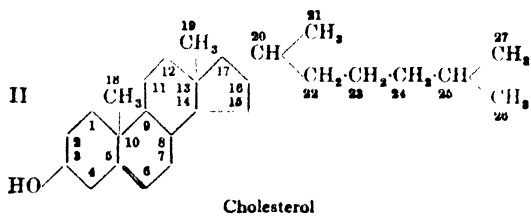
Butadiene is also made by cracking petroleum, and the rubber from this is termed SKA.

3. *Duprene* or *Neoprene*.—The basis is acetylene, and the first stage is the polymerization of this to vinylacetylene,  $\text{CH}_2\text{:CH}\cdot\text{C}\equiv\text{CH}$ , the second the addition of hydrogen chloride to form chloroprene, 2-chloro- $\Delta^{1,2}$ -butadiene,  $\text{CH}_2\text{:CH}\cdot\text{CCl}\text{:CH}_2$ , and finally the polymerization of this to duprene,  $(\text{C}_4\text{H}_5\text{Cl})_n$ . The first stage is accomplished by using a saturated solution of cuprous and ammonium chlorides; a certain amount of divinylacetylene is formed and also tar, which has no commercial value; in stage two there is a tendency for a second molecule of HCl to add on, forming a dichlorobutene. The third stage requires the greatest attention as the polymerization may proceed too far and materials of little value be formed. To prevent this the reaction is stopped while there is still some chloroprene present, and the material stabilized by the addition of a little phenyl-*p*-naphthylamine; the monomer can be removed by distillation or solution in ethyl alcohol, and the product is unvulcanized duprene. It is plastic, can be readily moulded, compounded with suitable fillers, e.g. carbon black, magnesia, oxide of zinc, rosin, cotton seed oil, &c., and can then be vulcanized with or without (oxygen vulcanized) the addition of small amounts of sulphur.

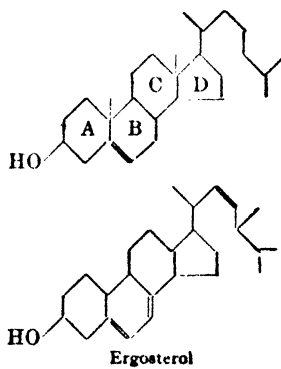
Duprene is not regarded as a substitute for rubber, as it is more costly to manufacture, but it is being utilized where natural rubber is of little use. Its main advantages compared with raw products are: (a) it is more resistant to abrasion; (b) not so readily oxidized or ozonized, and less susceptible to fatigue and cracking; (c) oils, vegetable, animal and mineral, produce less deterioration (Ind. Eng. Chem., 1933, 1219); (d) more resistant to high temperatures, to storage and to sunlight; (e) not so porous to gases, and has a lower water absorption.

On account of these properties it is used for balloon fabrics, printing rollers, high-tension cables, a non-corrosive lining for chemical plant, &c.

It has certain disadvantages, viz. disagreeable odour, darker colour and inferior electric properties. It itself will not form hard rubbers (ebonite) by exhaustive vulcanization, but a mixture of it with raw rubber yields an ebonite which is more pliable than ordinary ebonite.



or more simply,





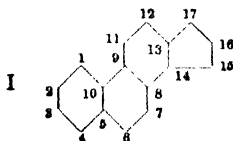


Chloroprene mixed with a solution of sodium oleate forms a synthetic latex, from which by rapidly stirring at 10° a theoretical yield of a completely vulcanized neoprene rubber is formed after 24 hours. This latex is of great value for coating fabrics or for impregnating porous materials.

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## LXII. NATURAL PRODUCTS DERIVED FROM CYCLOPENTENO-PHENANTHRENE. STEROIDS.\*

All these compounds contain the cyclopenteno-phenanthrene skeleton I, which is built up of three 6-membered and one 5-membered carbon ring. The numbering of the carbon atoms is given in the diagram.



### A. Sterols

The sterols and phosphatides are normal constituents of oils and fats in both the animal and vegetable kingdom. To isolate them the oil is saponified with alcoholic potash, and after removal of alcohol the unsaponified matter is extracted with ether or light petroleum. A given fat frequently gives a mixture of sterols which are extremely difficult to separate, especially those from vegetable oils. In the oil they may be present in the free state or as esters of fatty acids. Those derived from vegetable oils are termed **phytosterols** and those from animal fats **cholesterols**. A list of the commoner sterols is given in the table. All are crystalline and yield crystalline derivatives. The structure of a typical sterol is given in II, which represents cholesterol. This also illustrates the numbering of the carbon atoms in the side chains. All the sterols contain

\* L. F. Fieser, *Chemistry of Natural Products related to Phenanthrene*, 2nd Edition, New York, 1937; also Rep., 1933, 198; 1934, 206; 1936, 341.

an OH group in position 3 and Me substituents in positions 10 and 13. They differ, however, in their degree of unsaturation and also in the nature of the long side chain in position 17.

## COMMON STEROLS

Name	Formula	No. of double bonds	m.-pt.	$[\alpha]_D^\circ$	Source
Cholesterol ..	$C_{27}H_{46}O$	1	150	- 38.8	All animal cells, and is the chief cause of human gall-stones.
Dihydrocholesterol ..	$C_{27}H_{48}O$	0	142	+ 28.8	Do.
Coprosterol ..	$C_{27}H_{48}O$	0	102	+ 23.5	Fæces.
Ostreaosterol ..	$C_{29}H_{48}O$	2	143	- 43.9	Oysters.
Ergosterol ..	$C_{28}H_{44}O$	3	163	- 133	Ergot, yeast.
† $\beta$ -Sitosterol ..	$C_{29}H_{50}O$	1	—	—	Cotton seed oil.
$\gamma$ -Sitosterol ..	$C_{29}H_{50}O$	1	146	- 42.4	Fats of higher plants.
Stigmasterol ..	$C_{29}H_{48}O$	2	170	- 45	Calabar and Soya beans.
Cinchol ..	$C_{29}H_{50}O$	1	140	- 34	Cinchona bark.
Zmyosterol ..	$C_{27}H_{44}O$	2	110	+ 47	Yeast.

**Ergosterol** differs from cholesterol in having three olefine linkings, viz. 5 : 6 (same as cholesterol), 7 : 8, 22 : 23, i.e. in the long side chain, and an extra methyl substituent in position 24.

**Stigmasterol** has double bonds in positions 5 : 6 and 22 : 23, and an ethyl substituent in position 24, i.e. the side chain at 17 is  $\cdot CHMe \cdot CH : CH \cdot CHEt \cdot CHMe_2$ .

**Sitosterol** has the chain  $\cdot CHMe \cdot CH_2 \cdot CH_2 \cdot CHEt \cdot CHMe_2$ , but is otherwise identical with stigmasterol.

The completely reduced cholesterol is termed  **$\beta$ -cholestanol**, and the corresponding saturated hydrocarbon, obtained by removal of hydroxyl, as **cholestane**. The hydroxyl in these compounds is removed by conversion into the chloro-compound and subsequent reduction with amyl alcohol and sodium, and the double linkings are finally hydrogenated by palladium and hydrogen.

Theoretically a great number of structurally isomeric sterols

\* For relation between optical active and constitution, cf. *Callow and Young*, P. R. S., 1936, A., 167, 194.

† Identical with 22-dihydrostigmasterol.

are possible, but very few are known owing to the fact that both hydroxyl and methyl substituents retain the same positions in the different compounds. Structural isomerides are met with in the bile acids.

The sterols do not contain true aromatic rings, but partially or completely reduced rings.

The stereochemistry of the group is thus complicated and analogous to that of substituted decalins (Chap. L, A7).

1. On the one hand, there are the steric arrangements due to the fusion of two cycloparaffin rings as in decalin. This fusion may be of the *cis* or *trans* type, and as in the steroid skeleton there are three such fusions, viz. A and B rings, B and C, C and D rings, the number of possible variations is great. In practically all cases, however, the fusion in the two latter cases, i.e. rings B and C and C and D, are all of the same type, namely, *trans*-decalin type. An exception is the heart poison sarmentogenin with a B and C *cis* fusion. Hence cases of stereoisomerism are attributable to the *cis* and *trans* condensations of rings A and B.

The steroids can be divided into two main groups, viz. (a) a group represented by cholestane and including such compounds as allocholane, allopregnane, stigmasterol, ergosterol and sitosterol. In these the union of the two rings is of the *trans*-decalin type, with the result that the Me group in 10 and the H atom in 5 are *trans* to one another. (b) A group represented by coprostan (coprosterol with OH replaced by H) and containing cholane, pregnane and aetiocholane. The union of rings A and B is of the *cis*-decalin type, and the Me at 10 and H at 5 are *cis* to one another.

2. In nearly all cases steroids have an OH group in position 3, i.e.  $>\text{CH}(\text{OH})$ , and hence 3 is a point of dissymmetry, i.e. in all cases a normal and an epi configuration are possible. Considerable confusion has arisen as certain authorities classify the compounds as *cis* or *trans* when the OH is *cis* or *trans* to the H in 5,\* whereas others group them as *cis* or *trans* with respect to the Me group in 10, and it has been suggested that the two groups be termed ( $\alpha$ ) and ( $\beta$ ) (Fieser, p. 399). The ( $\beta$ ) group comprises cholesterol, dihydrocholesterol, coprosterol, ergosterol, whereas the epimerides or ( $\alpha$ ) group comprises most of the bile acids and androsterone.

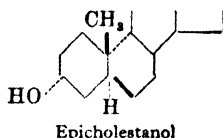
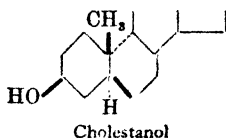
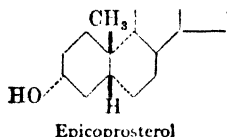
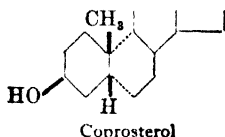
Practically all compounds of the ( $\beta$ )-type are precipitated

\* In steroids with a 5 : 6 olefine link there is no H atom at 5.

by digitonin, whereas the ( $\alpha$ )-compounds are not. The OH group in compounds of the  $\beta$ -type is remarkably labile and readily replaced by halogen, and the corresponding alkyl ethers are also labile and the OR group readily replaced by halogen. The esters, e.g. acetates and benzoates, of the ( $\beta$ )-group are also hydrolysed more readily than the epimeric ( $\alpha$ )-compounds. These differences may be due to spatial relationships in the two groups (Helv., 1938, 498; Bull. Soc., 1933, [IV], 53, 581).

Stereoisomerism due to the relative positions of the long side chain at 17 and the Me at 13 is also possible.

The method of representation of stereoisomerides is illustrated in the following formulæ (cf. *Miescher and Fischer*, C. and I., 1939, 113):



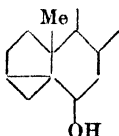
The unsaturated sterols give characteristic colour tests with acetic anhydride and sulphuric acid, acetyl chloride and zinc chloride, and with trichloroacetic acid.

Plants are able to synthesize sterols from simpler materials such as sugars, and the higher animals appear to synthesize their own cholesterol and not to obtain it from vegetable sterols, as these latter appear to be eliminated unaltered from the system.

An isomeric *allocholesterol* is known with the olefine link in position 4 : 5. It is formed together with its epimeride by the reduction of cholestenone (CO in 3 and olefine link in 4 : 5) with aluminium *isopropyl* oxide, and on reduction gives coprosterol indicating *cis* fusion of rings A and B. It is characterized by readily losing water yielding  $\Delta^{2:4}$ -cholestadiene.

Normal ethers of cholesterol are obtained by the action of alcohols on the chloride, bromide or *p*-toluenesulphonate of

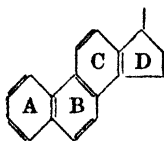
the sterol, whereas in the presence of potassium acetate an isomeric ether is formed derived from *i*-cholesterol, which is represented as having no olefine link but a bridge between C atoms 3 and 5 and the OH group in position 6:



**Structure of Cholesterol.**—The presence of one hydroxyl group is proved by the formation of esters such as a monoacetate and benzoate (1889), and that the OH is part of a secondary alcoholic group is proved by its oxidation to a ketone (1903). The presence of a double linkage is shown by the formation of a dihydride, a dibromide (1868), and a hydrobromide. From the hydrogen content of the completely saturated hydrocarbon (cholestane,  $C_{27}H_{48}$ ), it is clear that four saturated rings must be present termed A, B, C and D.

The structure of the side chain in position 17 has been proved as follows: When oxidized with chromic acid and steam distilled methyl isohexyl ketone is formed, the semicarbazone of which is identical with that of the synthetic ketone,  $CH_3 \cdot CO \cdot [CH_2]_3 \cdot CH(CH_3)_2$ , thus indicating that the side chain is  $\cdot CH(CH_3) \cdot [CH_2]_3 \cdot CH(CH_3)_2$ ; a second product of the oxidation is the ketone,  $C_{19}H_{30}O$ , which contains the ring skeleton of the sterol but with C No. 17 in the form of CO.

By dehydrogenation of the sterol with selenium at  $320^\circ$ , one of the products is a hydrocarbon,  $C_{18}H_{16}$ , termed *Diel's* hydrocarbon, and the structure of this has been shown by *Harper, Kon* and *Ruzicka* to be identical with that of synthetic 17-methylpentenophenanthrene:



In this reaction the three 6-ring systems are converted into true aromatic rings, the methyl substituents attached to tertiary carbon atoms, i.e. groups at junction of two rings are

eliminated, and the complex group,  $C_8H_{17}$ , is transformed into a methyl group. The position of the  $C_8H_{17}$  group at  $C_{17}$  is thus proved, and also the position of the other substituents either two methyl or one ethyl at ring junctions is indicated, as they would not be removed if present as  $>CH\cdot CH_3$  groups in the sterol.

**Relationship of Cholesterol, Ergosterol and Stigmasterol.**—Each sterol is separately acetylated, the olefine linkages hydrogenated, and the product oxidized with chromic acid. If X denotes the fully hydrogenated 4-ring system with OH in 3 and Me in 10 and 13, then dihydrocholesterol,  $X\cdot CHMe\cdot CH_2\cdot CH_2\cdot CH_2\cdot CHMe_2$ , in the form of its acetyl derivative, gives as oxidation product 3-hydroxyallocholanolic acid,  $X\cdot CHMe\cdot CH_2\cdot CH_2\cdot CO_2H$ , and this by *Wieland's* process of degradation, i.e. conversion into the tertiary alcohol  $X\cdot CHMe\cdot CH_2\cdot CH_2\cdot CPh_2\cdot OH$  by the action of phenyl magnesium bromide on the methyl ester and subsequent oxidation, yields benzophenone and hydroxynorcholanolic acid,  $X\cdot CHMe\cdot CH_2\cdot CO_2H$ . This last product is formed when tetrahydrostigmasteryl or hexahydroergosteryl acetates are directly oxidized, and thus prove that the hydroxy, methyl and complex side chain occupy the same positions in all three compounds, and that the additional C atoms in these two compounds are present as methyl and ethyl respectively in position 24, as they are eliminated during oxidation with the terminal carbon atoms of the long chain as ketone  $CH_3\cdot CO\cdot CHMe_2$  and  $CH_3\cdot CH_2\cdot CO\cdot CHMe_2$  respectively, or as the corresponding aldehydes on ozonolysis.

## B. Bile Acids

Human bile contains inorganic salts, sodium salts of conjugated bile acids, small amounts of cholesterol, lecithin, and bile pigments—among the most important of which is **bilirubin**, an oxidation product of hæmin. It is produced in the liver and stored in the gall bladder, and the bile salts have the property of keeping substances insoluble in water in a state of solution or dispersion. After alkaline hydrolysis the bile yields the bile acids—usually a mixture of several.

The table gives a list of the more important bile acids.

## BILE ACIDS

Name	Formula	Positions of OH groups	m.-pt.	$[\alpha]_D$	Sources
Cholic acid ..	$C_{24}H_{40}O_5$	3:7:12	195	+37	Man, ox, goat, sheep.
$\beta$ -Phocaecholic ..	"	3:7:22	222	+28	Walrus, seal.
Nutriacholic ..	"	—	198	+5.5	Swamp beaver.
Bufodesoxycholic ..	"	3:7:12	—	—	Toad (with a side chain similar to that in ergosterol).
Desoxycholic ..	$C_{24}H_{40}O_4$	3:12	176	+11	Same as cholic.
Chenodesoxycholic ..	"	3:7	140	—	Man, ox, goose, hen.
Ursodesoxycholic ..	"	3:7	198	—	Bear.
Hyodesoxycholic ..	"	3:6	197	—	Hog, hippopotamus.
$\alpha$ -Lagodesoxycholic ..	$C_{24}H_{40}O_4$	3:12	156	—	Rabbit: Stereoisomeric with desoxycholic.
Lithocholic ..	$C_{21}H_{40}O_3$	3	186	+32	Man, ox, &c.



These acids are present in the bile as peptide-like compounds with glycine and taurine, from which they are liberated by alkaline hydrolysis.

In hyodesoxycholic and lithocholic acid and probably in most bile acids the OH in 3 is *trans* with respect to Me in 10, i.e. they belong to the epicoprosterol series, and probably the OH in 7 is in *trans* positions to Me at 10 in cholic and chenodesoxycholic acids (B., 1935, 766, 1814).

All the acids contain one carboxylic group and one or more hydroxy groups in the form  $\cdot\text{CH}\cdot\text{OH}$ .

They all contain the same 4-ring skeleton as the sterols, but are free from olefine linkages. The corresponding saturated hydrocarbon is  $\text{C}_{23}\text{H}_{40}$ , *cholane*, and the acid *cholanolic acid*,  $\text{C}_{23}\text{H}_{39}\cdot\text{COOH}$ . When the bile acids are heated under reduced pressure, 1, 2 or 3 molecules of water are eliminated according to the number of hydroxyl groups present, and unsaturated acids, usually a mixture of isomerides with 1, 2 or 3 olefine linkages, are formed, but these are readily hydrogenated, yielding cholanic acids. In cholanic acid derived from common bile acids the rings A and B are in the *cis*-decalin positions, whereas when hyodesoxycholic acid is dehydrated and then hydrogenated, the product is *allocholanic acid* (i.e. the *trans*-decalin type), although the hyodesoxycholic acid appears to be of the *cis* type.

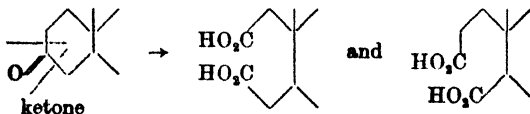
Desoxycholic acid forms very stable additive or co-ordination compounds with fatty acids and also with esters, alcohols, ethers, phenols and even paraffin hydrocarbons. These are termed *cholic acids*, and the number of molecules combining with 1 of the bile acid varies from 1 in the case of acetic to 8 in the case of palmitic and higher fatty acids.

The close relationship between the sterols and the bile acids was established by *Windans* (1919), who, on gently oxidizing the saturated hydrocarbon, cholestane, obtained from cholesterol, was able to isolate *allocholanic acid*, and by subjecting coprostanol, which is stereoisomeric with cholestane, to the same treatment, cholanic acid, the parent substance of the bile acids, was obtained. In this oxidation the terminal isopropyl group of the side chain of the sterol hydrocarbon is removed as acetone, and the  $\text{CH}_2$  group adjacent is oxidized to  $\text{CO}_2\text{H}$ . This furnished a proof of the presence of the group  $\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  in position 17 in cholanic acid and the bile acids generally, and also of the presence of the same 4-ring system in the bile acids as in the sterols.

Lithocholic acid can be obtained from cholesterol (J. Biol. Chem., 1936, **115**, 19), an intermediate being 3-hydroxy- $\Delta^5$ -cholanolic acid.

The isolation of *Diel's* hydrocarbon and its synthesis can be claimed to have established the structure of the 4-ring skeleton of the sterols and bile acids, but considerable evidence had previously been advanced indicating the same structure.

All reduced sterols and all bile acids contain one or more  $\cdot\text{CH}\cdot\text{OH}$  groups as part of a ring. Such secondary alcoholic groups are readily oxidized by suitable oxidizing agents to cyclic ketones—each  $\text{>CH}\cdot\text{OH}$  group in its turn yielding  $\text{>CO}$ ; but in all reactions of the secondary alcoholic groups, e.g. acylation, hydrolysis, oxidation, there is a graduation in the positions numbered 3, 7 and 12, the 3 position being the most active. When one of these ketones is further oxidized with concentrated nitric acid or permanganate the ring is ruptured, and all cholic acids under this treatment yield a mixture of two tribasic acids which are usually termed *bilianic acids*; thus desoxycholic acid  $\rightarrow$  monoketone  $\rightarrow$  desoxybilianic acid and *iso*-desoxybilianic acid. The formation of two structurally isomeric acids indicates (a) that the ketonic ring has been broken at two points, (b) that the ketone is present as  $\text{—CH}_2\cdot\text{CO}\cdot\text{CH}_2\text{—}$  in the ring; otherwise if it were  $\text{>CH}\cdot\text{CO}\cdot\text{CH}_2\cdot$  with one carbon attached to an alkyl group or to a second ring in addition to forming part of the original ring, one oxidation product would be a ketone. The formulæ for the two acids, since the 3 position is first oxidized, would be:



Evidence as to the size of the ketone ring from which the two acids were formed is afforded by an examination of the cyclic compound obtained on heating the acids, viz. ketones or anhydrides. According to *Blanc's* rule (C. R., 1907, **144**, 1356) only 1 : 6-dibasic acids\* yield cyclic ketones on heating; 1 : 3-, 1 : 4- and 1 : 5-dibasic acids yield anhydrides. Thus the bilianic acids must be 1 : 6 acids of the type  $\text{HO}_2\cdot\dot{\text{C}}\cdot\dot{\text{C}}\cdot\dot{\text{C}}\cdot\dot{\text{C}}\cdot$

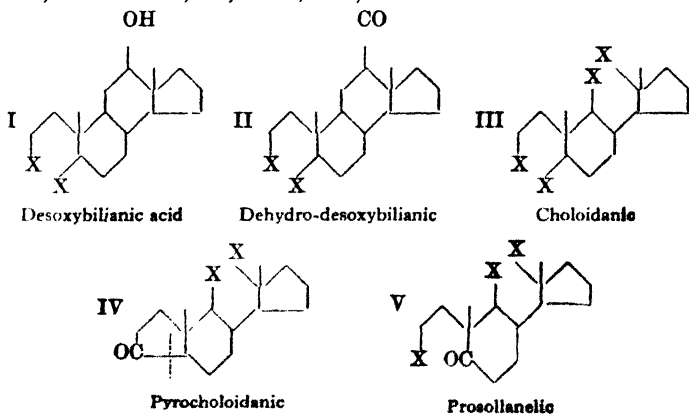
\* In the numbering the C atoms of the carboxylic groups are included.

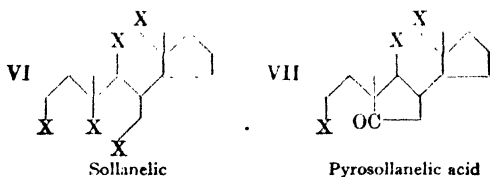
$\dot{C}\cdot\text{CO}_2\text{H}$ , and the original ketone must have been a six-membered cyclic ketone. This proves that one ring (viz. the one marked A on p. 1105) is a six-carbon ring, is attached to only one other ring, and must contain the OH in position 2 or 3. Further careful study has favoured the 3 rather than the 2 position. Dihydrocholesterol behaves in exactly the same manner, the only point of difference being the relative proportions of the two bilianic acids formed on oxidation.

This method of examination, viz. oxidation of the secondary alcohol to a ketone, the oxidation of these to dibasic acids, and the cyclization of these has been extended to the other rings present in the 4-ring skeleton.

The method as applied to ring B in desoxycholic acid is indirect, as there is no OH substituent in this ring, and is shown in the following scheme where  $\text{X} = \text{CO}_2\text{H}$ .

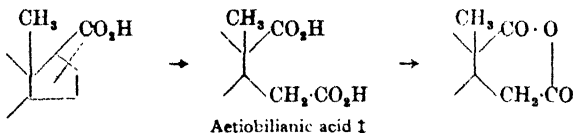
The first product of oxidation is desoxybilianic acid (I), obtained by rupture of ring A. Further oxidation converts the  $\text{CH}\cdot\text{OH}$  group of ring C into  $\text{CO}$  (II), and still further oxidation ruptures ring C, giving a tetrabasic acid (III). On heating ring closure occurs, and a new cyclic ketone (old ring A) is formed (IV), and this on oxidation gives the ketonic ( $\text{CO}$  in ring B) tribasic acid (V) by rupture of the ketone ring. On still further oxidation ring B is ruptured, and a pentacarboxylic acid, sollanelic acid (VI), is formed, and this when heated yields a ketonic tribasic acid (VII), indicating that the last ring ruptured (B) is a 6-carbon ring (for confirmation, cf. *Borsche, B.*, 1927, 723).





In 1926 *Wieland* succeeded, by starting with cholanic acid which contains no hydroxyl groups, in oxidizing ring D and proving that it is a 5-membered carbon ring. The method was the degradation process of converting an ester into a tertiary alcohol by means of a *Grignard* compound, and oxidizing this to a ketone and an acid containing one atom of carbon less than the original acid.

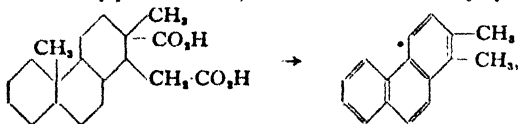
Thus methyl cholananate,  $X \cdot CHMe \cdot CH_2 \cdot CH_2 \cdot CO_2Me$ ,\* gives the tertiary alcohol  $X \cdot CHMe \cdot CH_2 \cdot CH_2 \cdot CMe_2 \cdot OH$ , which is oxidized by chromic acid to acetone and  $X \cdot CHMe \cdot CH_2 \cdot CO_2H$ . The process is repeated, using the methyl ester and phenyl magnesium bromide and oxidizing the diphenylcarbinol,  $X \cdot CHMe \cdot CH_2 \cdot CPh_2 \cdot OH$ , to  $COPh_2$  and  $X \cdot CHMe \cdot CO_2H$ . The latter can yield  $X \cdot CHMe \cdot CPh_2 \cdot OH$ , which by loss of water gives  $X \cdot CMe : CPh_2$  and on oxidation  $COPh_2$  and  $X \cdot CO \cdot Me$ , and finally  $X \cdot CO_2H$  *aetiocolanic acid*.† This acid on further oxidation undergoes fission in ring D and a dibasic acid is formed, which when heated yields a cyclic anhydride. Hence the acid cannot be a 1 : 6-dibasic acid, but probably a 1 : 5-acid, and hence the original ring D a 5-membered carbon ring.



\* X represents the saturated 4-ring skeleton free from hydroxyl groups.

† This series of reactions proves the structure of the side chain, particularly the position of the Me group.

‡ This acid is of further interest as when dehydrogenated with selenium it yields 1:2-dimethylphenanthrene, which has been directly synthesized,



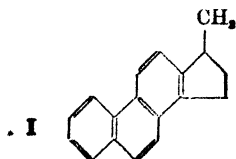
thus confirming the presence of a methyl group in the bile acid molecule in position 13.

When *Blanc's* rule is applied to the acids obtained by the fission of ring C, the result indicates that this is a 5-membered ring, and for several years formulæ for desoxycholic acid were represented as made up of two 6- and two 5-membered rings, but such formulæ were abandoned as the result of X-ray examinations, and also as a result of the establishment of the structure of *Diel's* hydrocarbon,  $C_{18}H_{16}$  (p. 1105), and in 1932 *Rosenhain* and *King* suggested the formula which is now generally accepted for desoxycholic acid, viz. three 6-membered carbon and one 5-membered carbon ring with OH substituents in 3 and 12, methyls in 10 and 13, and the complex side chain  $\cdot CHMe \cdot CH_2 \cdot CH_2 \cdot CO_2H$  in 17.

*Blanc's* rule appears to hold good for all open-chain dibasic acids and for acids derived from a monocyclic compound, but not when the carboxylic groups are attached to a carbon chain which connects two ring systems.

The fact that chrysene (Chap. XXXII, C.) is one of the products obtained by the selenium dehydrogenation of sterols and bile acids led *Rosenhain* and *King* to suggest a 6-carbon system for ring D, but this was discarded in 1932, and it was generally accepted that in the formation of chrysene during pyrolysis an opening of the five C ring occurs followed by a closing to form a six C ring.

The synthesis of 3'-methyl-cyclopenteno-phenanthrene I by *Bergmann* and *Hilleman* (B., 1933, 1302) and by *Harper*, *Kon* and *Ruzicka* (J. C. S., 1934, 124), and the proof that this compound is identical with *Diel's* hydrocarbon, viz. by comparison of X-ray photographs, the formation of the characteristic nitroso-compound melting at  $238^\circ$ – $239^\circ$  and the tribromo-derivative melting at  $235^\circ$  (1935, 644) may be regarded as having settled the structure of the sterol and bile acid skeleton.



### C. Ergosterol and Calciferol (Vitamin D<sub>2</sub>)

**Ergosterol**, C<sub>28</sub>H<sub>44</sub>O, has the same 4-ring skeleton as cholesterol, but has three olefine linkings and an extra methyl group. It was first prepared from ergot, but is now usually obtained from yeast, and is a compound of great interest on account of its relationship to vitamin D. The following points help in the elucidation of its structure. (1) When subject to ozonolysis one of the products is methyl-isopropyl-acetaldehyde, CHMe<sub>2</sub>·CHMe·CH:O, which indicates a double linking at position 22 : 23 and the extra methyl group in 24 (cf. formulæ opposite p. 1101),



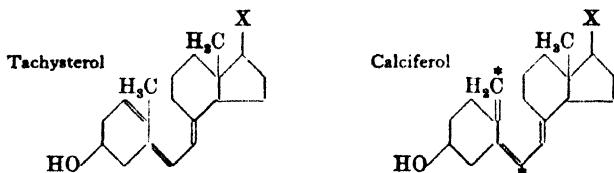
The conjugate position of the remaining double bonds is proved by the formation of an additive compound with maleic anhydride, and also by its absorption spectrum and molecular refraction. As *Windans* (A., 1930, **481**, 127) has shown that one olefine linkage is in the same position as in cholesterol, viz. 5 : 6, the other must be in position 7 : 8.

A further proof of the position of these two double bonds is afforded by the dehydrogenation of neoergosterol (ergosterol minus the methyl in position 10) to a phenol with a naphthalene system (A., 1934, **511**, 292), indicating the removal of hydrogen from A in order to yield the phenolic OH and from B and not C to yield the second ring of the naphthalene system. The Δ<sup>5:7</sup> and not Δ<sup>6:8</sup> positions of the links is proved by the oxidation of ergosterol with perbenzoic acid and subsequent hydrolysis when ergostadienetriol is obtained, which is readily hydrogenated to ergostanetriol with 3OH in 3, 5 and 6, indicating the presence of the one link in position 5 : 6, and as the other is conjugate it must be 7 : 8.

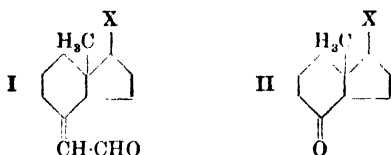
Many oils when exposed to sunlight or ultra-violet light attain anti-rachitic properties similar to fish liver oils containing vitamin D. This was attributed to a change in the cholesterol constituent of the oil, but later ergosterol was regarded as the provitamin, as this sterol when irradiated acquires physiological activity, and careful investigation has shown that a whole series of changes occurs during irradiation, viz. 1 ergosterol → 2 lumisterol → 3 tachysterol → 4 calciferol → 5 toxisterol → 6 suprasterols. All changes are intramolecular,

so all these compounds have the same molecular formula  $C_{28}H_{44}O$ . For some time it was thought that the only change taking place was a gradual shifting of the olefine linkages from ring A to ring D, so that the whole series had the same 4-ring skeleton. More detailed examination has shown that there is a marked similarity between the first two compounds in both physical and chemical properties, and similarly with the third and fourth compounds, but that there are marked differences between the two pairs. Thus 1 and 2 have very similar ultra-violet absorption spectra with a definite band at 250–300, they both contain three olefine bonds, and both give *Diel's* hydrocarbon on dehydrogenation; 3 and 4, on the other hand, have a much more intense absorption band in the same position; they can be shown to contain four olefine bonds by  $H_2$  absorption, and do not yield *Diel's* hydrocarbon on dehydrogenation.

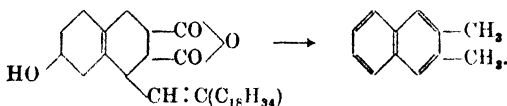
All compounds appear to contain the same side chain at 17, with an olefine link at 22 : 23. Lumisterol and ergosterol are probably stereoisomeric, the former being the epiform of the latter (with reference to the No. 10 methyl group). The former is not precipitated by digitonin (J. C. S., 1935, 1221; B., 1935, 539). The change which occurs at the second stage, viz. lumisterol  $\rightarrow$  tachysterol, must involve a fission of a ring, viz. B, and the formation of a fourth olefine link, whereas the third change involves the shifting of an olefine link:




The presence of conjugated olefine linkages in both these formulæ is compatible with the high absorption shown by both compounds. The above formula for calciferol, which was first suggested by *Heilbron* (C. and I., 1935, 195), is largely based on the following reactions: oxidation with chromic acid yields an unsaturated aldehyde  $C_{21}H_{34}O$  and a saturated ketone  $C_{19}H_{34}O$ , the structures of which are represented by I and II:



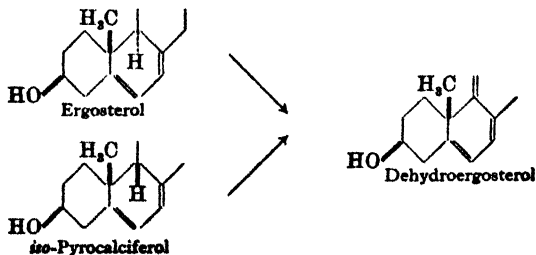
Calciferol forms an additive compound with maleic anhydride (at the carbon atoms marked \*), and this can be converted into 2:3-dimethylnaphthalene (structure proved by synthesis) by selenium dehydrogenation:



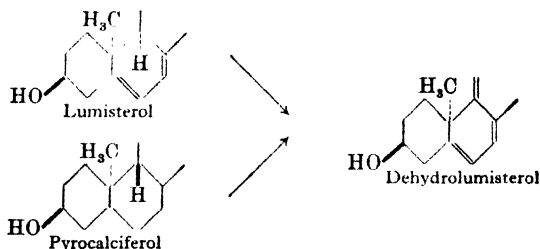
The latter reaction is interesting as it involves the conversion of  into two methyl groups, but other examples of the same type are known.

Calciferol yields a definite crystalline 3:5-dinitrobenzoate.

By the action of heat on calciferol two products, isopyrocalciferol and pyrocalciferol, are formed. The former when oxidized with mercuric acetate yields the same dehydroergosterol as is obtained by oxidizing ergosterol, and hence the two sterols are stereoisomeric and differ only with respect to  $C_9$ . Similarly lumisterol and pyrocalciferol yield the same dehydrolumisterol on oxidation and are stereoisomeric. The two pyro-compounds differ from one another in the steric arrangements of the  $C_{10}$  methyl group, in exactly the same manner as do ergosterol and lumisterol (*Dimroth*, B., 1936, 1123; cf. J. C. S., 1939, 250).







For several years it was thought highly probable that calciferol ( $D_2$ ) was identical with the vitamin D present in fish liver oils, but it was found that the natural product was superior to  $D_2$  in its curative effects on rachitic chicks.

It has been shown that 7-dehydrocholesterol\* (i.e. ergosterol with the unsaturated side chain replaced by the saturated chain of cholesterol, viz.  $\cdot\text{CHMe}(\text{CH}_2)_3\cdot\text{CHMe}_2$ ) when irradiated yields a product showing exactly the antirachitic activity and absorption bands as the natural vitamin and has been isolated as its 3:5-dinitrobenzoate melting at  $128.5^\circ$ . It has been termed vitamin  $D_3$ , and by a series of solution between two solvents and of fractional chromatographic absorption on alumina has been isolated from tunny liver oil and halibut liver oil (Z. physiol., 1936, 241, 104; J. A. C. S., 1936, 2155) and characterized as the dinitrobenzoate melting at  $128.5^\circ$ .

### D. Sex Hormones †

The male and female sex hormones referred to in Chap. LXVIII, B., form another group of compounds containing the same 4-ring system as the sterols and bile acids.

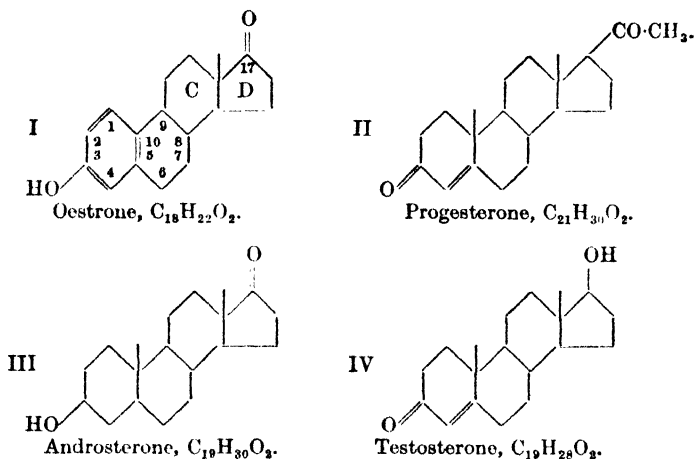
The formulæ I-IV for the four common hormones illustrate

\*  $\Delta^5:7$ -Cholestadien-3-ol is present in pigskin and can be prepared by the following series of reactions:

Cholesteryl acetate with chromic acid gives the  $\cdot\text{C}=\text{O}$  group in position 7, and this reduced with aluminium isopropoxide gives  $\cdot\text{CH}(\text{OH})$  in the same position, and by the hydrolysis of the acetate a similar group in position 3, i.e. 3:7-dihydroxycholest-5-ene, and the dibenzoyl derivative of this when heated loses a molecule of benzoic acid and yields the benzoyl derivative of  $\Delta^5:7$ -cholestadien-3-ol, i.e. the benzoyl derivative of a compound differing from ergosterol by the absence of a double linkage in the side chain at 17.

† *Butenandt*, C. and I., 1936, 990; Rep. 1936, 360; 1938, 300.

some of the more important structural differences between these hormones and the sterols.

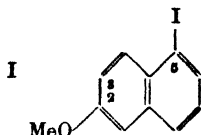


Although they all contain the same 4-ring skeleton and the methyl groups in 10 or 10 and 13, some contain  $\cdot CH(OH)$  in 3 and others  $\cdot C:O$  in this position as part of the ring, and all are devoid of a long side chain at 17. The degree of unsaturation varies considerably, but any olefine linkages (1 or 3) occur in ring A.

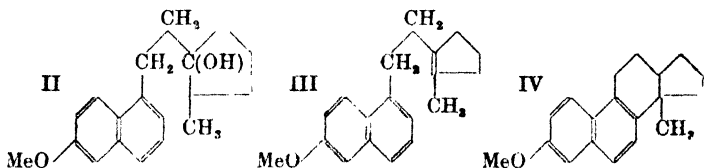
**Oestrone**,  $C_{18}H_{22}O_2$ , the follicular hormone, is a hydroxy ketone with three olefine linkages in the rings, and the elucidation of its structure is largely due to *Butenandt*. When oxidized the ring (D) containing the carbonyl group is ruptured, a dibasic acid is formed, and when this is heated it yields an anhydride and not a ketone, and hence the original ring was a 5-carbon and not a 6-carbon ring. The formation of 1:2-dimethylphenanthrene—which has been synthesized by *Haworth's* method (Chap. XXXII, B2.)—by the selenium dehydrogenation of the dibasic acid indicates that the 5-carbon ring is attached to the phenanthrene system in the position 1:2. The given formula is also supported by unimolecular film measurements. The 3-position of the hydroxylic group follows from the relationship between the sterols and sex hormones, and the fact that the hydroxyl is phenolic and not alcoholic indicates the presence of at least one of the olefine linkages in this ring.

The following synthetical reactions are of value in discussions on the structure of oestrone:

(1) Starting with 5-nitro-2-naphthylamine and replacing the  $\text{NH}_2$  by  $\text{OH}$ , methylating and then replacing the  $\text{NO}_2$  by  $\text{I}$  through the intermediary of the amine, the product (I) is obtained. This is converted into the *Grignard* compound, and

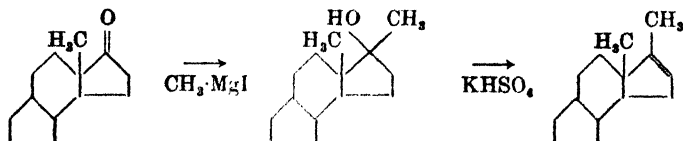


then condensed with ethylene oxide, yielding 2-methoxy-5-hydroxyethyl-naphthalene,  $\text{OMe} \cdot \text{C}_{10}\text{H}_6 \cdot \text{CH}_2\text{CH}_2\text{OH}$ . This is converted into the chloride and this into the *Grignard* compound, which condensed with 2-methyl-cyclopentan-1-one gives the alcohol (II). On heating this loses water yielding the unsaturated compound (III), which on ring closure gives the

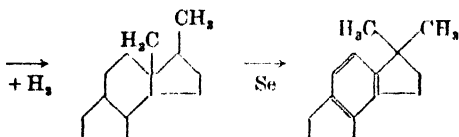


4-ring system (IV), which can be dehydrogenated by selenium to 7-methoxy-1:2-cyclopentenophenanthrene\* (yield only 0.04 per cent of the naphthalene compound used), which is also formed by converting oestrone into its methyl ether, reducing and dehydrogenating. Hence the 4-ring system and the position of the hydroxyl group are confirmed (*Cook* and others, *J. C. S.*, 1934, 653; cf. *ibid.* 864).

(2) Starting with oestrone methyl ether and carrying out the reactions indicated:

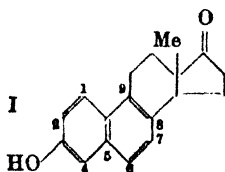


\* The angular Me is eliminated.



when the final product is 7-methoxy-3':3'-dimethyl-1:2-cyclopentenophenanthrene. In the last reaction the methyl group in position 13 passes during dehydrogenation into position 17 in the 4-ring system, a reaction which has been met with in other cases and may be regarded as a confirmation of the 13 position of the methyl group in the original hormone.

The two hormones equilin, C<sub>18</sub>H<sub>20</sub>O<sub>2</sub>, and equilenin, C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>, yield the same product when treated as above, and hence these compounds have their OH, Me and CO groups in the same positions, viz. 3, 13 and 17, and as equilenin forms a well-defined picrate it appears to be a true naphthalene derivative with the structure I, and equilin, which contains one olefine link less, is represented as having a double bond in position 7:8, but single bonds in 6:7 and 8:9 (Cook and Roe, C. and I., 1935, 501).

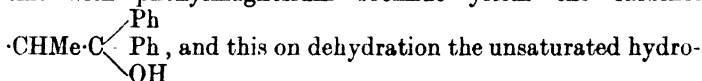


Compounds closely related to equilenin have been synthesized by Robinson (J. C. S., 1938, 1390, 1994).

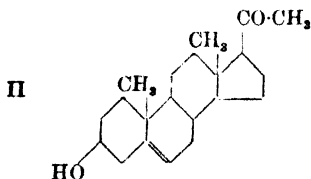
Oestradiol, C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>, is the secondary alcohol corresponding with the ketone oestrone, and oestriol, C<sub>18</sub>H<sub>24</sub>O<sub>3</sub>, is the 16-hydroxy oestradiol.

Progesterone, C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>, the hormone of the corpus luteum, is an unsaturated diketone, and its ultra-violet absorption spectrum indicates that the olefine link is in the αβ-position with respect to one carbonyl group, and the formula II (p. 1117) suggested by Slotta (1934) has been confirmed by Fernholz (1935), who prepared it from the plant sterol stigmasterol (p. 1102).

Stigmasterol is converted into its acetyl dibromide to protect both the hydroxyl group and the olefine linkage in ring B; it is then subjected to ozonolysis, the product is debrominated with zinc and hydrolysed, and in this way the complex chain at position 17 in stigmasterol is converted into the simpler group  $\cdot\text{CHMe}\cdot\text{CO}_2\text{H}$ . The methyl ester of this with phenylmagnesium bromide yields the carbinol



carbon  $\cdot\text{CMe}:\text{CPh}_2$ . Then by acetylating to protect the OH in position 3, and adding bromine to positions 5:6, oxidizing the group in position 17 to  $\cdot\text{CO}\cdot\text{CH}_3$  (and benzophenone), followed by debrominating and hydrolysing, the ketone  $\Delta^5$ -pregnene-3-ol-20-one\* (II), is formed, and when the dibromide is oxidized the  $\text{CH}\cdot\text{OH}$  in position 3 gives a CO group, and on debromination with zinc and acid the olefine linkage wanders into the 4:5 position to become conjugate with the C:O group in position 3. (N.B. by debromination in neutral solution it is possible to avoid this wandering of the double bond.)



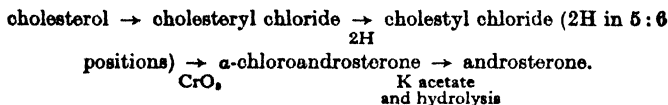
**Androsterone**,  $\text{C}_{19}\text{H}_{30}\text{O}_2$ , has a completely saturated ring system, with a secondary alcoholic  $\cdot\text{CH}(\text{OH})\cdot$  and a carbonyl group in the rings. Its structure follows from its formation from epidihydrocholesterol. Dihydrocholesteryl acetate when oxidized with chromic acid in glacial acetic acid solution yields a ketone stereoisomeric with androsterone and possessing similar physiological properties (*Ruzicka*, *Helv.*, 1934, 1389; 1935, 1407), and by substituting the acetyl derivative of epidihydrocholesterol† a small amount of androsterone is formed. The oxidation consists in completely removing the

\* The saturated hydrocarbon is termed pregnane.

† H and OH of the  $\cdot\text{CH}(\text{OH})\cdot$  group in epi positions compared with these groups in dihydrocholesterol.

side chain and converting  $>\text{CH}\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{CHMe}_2$  into  $>\text{C}:\text{O}$ .

A somewhat similar method has been used by *Marker* (J. A. C. S., 1935, 1755, 2358) by replacing the OH by chlorine instead of acetylating. The stages are:

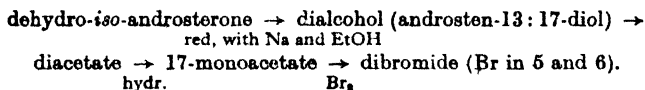


In this case, as cholesterol belongs to the normal and androsterone to the epi series with respect to carbon No. 3, a *Walden* inversion must have taken place.

Accompanying androsterone in nature is the active hormone *dehydro-iso-androsterone*,  $\text{C}_{19}\text{H}_{28}\text{O}_2$ , i.e. a compound with an olefine link in position 5:6 and with the OH in 3 in the normal position, also a third hormone, *androstandione*,  $\text{C}_{19}\text{H}_{28}\text{O}_3$ , similar to androsterone but with CO in place of CH(OH) in position 3.

Dehydro-*iso*-androsterone has been prepared from cholesterol in exactly the same manner as progesterone from stigmasterol (p. 1120), hence the  $\beta$ -position of the OH in 3.

**Testosterone**,  $\text{C}_{19}\text{H}_{28}\text{O}_2$  (IV, p. 1117), isolated in 1935, is an  $\alpha\beta$ -unsaturated ketone; it is unstable towards alkalis and physiologically is about 10 times as active as androsterone. Its structure follows from the following series of reactions:

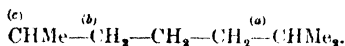


This oxidized, debrominated and hydrolysed gives testosterone. Here again a shifting of the double bond to the 4:5 position occurs during debromination. This gives a method for preparing testosterone from cholesterol.

Slight changes in structure of the testosterone molecule affect its activity. A 17-methyl ether has much the same activity as the original ketone, whereas the corresponding ethyl, vinyl and allyl compounds are inactive. A compound isomeric with testosterone but with the opposite configuration at 17 has only a small hormonal activity, and a shifting of the double

bond to the 5:6 position lessens the activity. In a series of esters of testosterone, it is found that an increase in the number of carbon atoms in the acyl group diminishes the activity as measured by comb growth in the cock, but increases its activity as measured by the rat test.

It has been suggested that bile acids and the sex hormones may possibly be derived from cholesterol in the animal system by oxidation at the points *a*, *b* and *c* in the 17-side chain



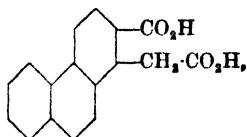
Oxidation at (*a*) would give the bile acids accompanied by hydrogenation in ring B and introduction of one or more OH groups. Oxidation at (*b*), followed by oxidation of CH-OH at 3 and a shifting of the olefine link from 5:6 to the 4:5 position, would give progesterone, and this by the addition of 6H gives pregnanediol and its isomeride. Oxidation at (*c*) produces dihydroandrosterone, and by oxidation and subsequent reduction testosterone and androsterone are formed, or by loss of CH<sub>2</sub> and dehydrogenation oestrone, and from this equilin by loss of 2H and equilenin by loss of 4H.

It has also been suggested that the ring skeleton of the sterols with the long side chain at 17 may be formed by the cyclization of carotene (Chap. LXIV, A1) and its degradation (*Bryant*, C. and I., 1935, 907, 1082; cf. Conversion of squalene into a tetracyclic compound, *Ruzicka*, *Helv.*, 1932, 431).

A glance at the formulæ of the chief sex hormones shows that they are closely related, and it has been found possible by relatively simple chemical methods to change a male hormone into a compound with follicular hormone properties. Thus the introduction of a CO group in place of the CH<sub>2</sub> in position 6 of testosterone produces a compound with properties similar to those of oestrone, and the introduction of a Δ<sup>1</sup>-link in the male hormone, androstandione, changes it from a male to a female hormone. Much work is now being carried out to establish relationships between structure and physiological activity on these types of compounds (cf. *Rep.*, 1938, 289).

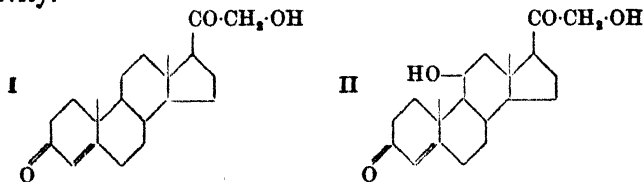
Many compounds of the 4-ring type (cholane skeleton) have the physiological properties of the follicular hormone;

others with a 3-ring system, e.g. the acid formed by the fission of the 5-membered ring D, have similar properties,



as have also (a) 1-keto-1:2:3:4-tetrahydrophenanthrene, (b) a derivative of 1:2:5:6-dibenzanthracene (Chap. LXIII) with OH and  $C_3H_7$  in para positions in the middle ring. On the other hand, the isomeric 4-ketotetrahydrophenanthrene is inactive. None of these compounds has physiological activity similar to that of androsterone. Of synthetic compounds with properties similar to those of oestrone the most interesting are the 4:4'-dihydroxy derivatives of *s*-diphenylethane and *s*-diphenylethylene (stilbene). The ethane derivative has only slight activity, but the introduction of the double link increases the activity considerably, and the compound with the greatest activity appears to be 4:4'-dihydroxy- $\alpha\beta$ -diethylstilbene,  $OH \cdot C_6H_4 \cdot CEt : CEt \cdot C_6H_4 \cdot OH$ . A dimeride of *p*-hydroxypropenylbenzene,  $OH \cdot C_6H_4 \cdot CH : CH \cdot CH_3$ , has an activity comparable with that of oestrone (Nature, 1937, **139**, 627, 1069; 1938, **141**, 78, 247).

**Hormones of Adrenal Cortex.\***—Cortin is the hormone of the adrenal cortex, and its function is to regulate and maintain the normal quantity of fluid in the vascular system. A crystalline compound obtained from cortin is corticosterone I, which is closely related to 21-hydroxyprogesterone II. This latter can be prepared from stigmasterol and shows distinct cortical activity.

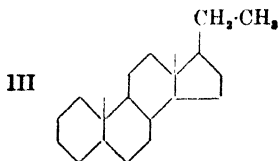


Corticosterone is readily converted into *allopregnane* III by the following stages: (1) Reduction of both CO groups to

\* Winterstein and Smith, Ann. Rev. Bio., 1938, 253; Miescher, Angew. Chem., 1938, 551.



CH·OH. (2) Oxidation of the 17 side chain  $\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{OH}$  to CHO. (3) Reaction of the  $\cdot\text{CHO}$  with  $\text{CH}_3\text{MgBr}$  yielding the side chain  $\cdot\text{CH}(\text{OH})\cdot\text{CH}_3$ , the oxidation of the three CH·OH groups to CO, and by the action of zinc mercury couple the reduction of the three CO groups to  $\text{CH}_2$ .



### E. Heart Poisons

To the cardiac poisons belong the most active constituents of the digitalis group, the strophanthins, periplocin from *Periploca gracea*, cymarin from *Apocynum cannabinum*, and uzarin from uzarin root. Some of these are used by natives as arrow poisons and some as medicinal compounds, especially as heart stimulants. Very small doses injected intravenously revive the heart action and lead to strengthening the contraction without altering the frequency. They also act on the blood vessels and increase the blood pressure.

They are all complex glycosides and on hydrolysis yield a sugar or mixture of sugars and hydroxypolynuclear compounds—allied to bile acids and termed **genins** or **aglycones**. The best-known compounds are those derived from the purple foxglove, *Digitalis purpurea*. The crystalline glycoside *digitalin* was isolated as early as 1869, and later from the same plant and from *D. lanata* the glycosides *digitoxin*, *gitoxin*, and *digoxin* were isolated and the structures worked out by *Jacobs* (1922–34). *A. Stoll* (1933–35) was able to show that these are the partial hydrolytic products of the actual glycosides present in the plant tissues, and that these latter glycosides can be isolated if the enzymes present in the tissue are first destroyed.

Three of these complex glycosides, digitanides A, B and C, have been isolated.

A on partial hydrolysis gives digitoxin, and on complete hydrolysis digitoxigenin with digitose (3 mols.), glucose and acetic acid.

B gives gitoxin, and finally gitoxigenin with the same sugars and acetic acid.

C gives digoxin, and finally digoxigenin with the same sugars and acetic acid.

The sea onion (*Scilla maritima*) and species of strophanthus, e.g. *S. kombe*, yield strophanthin  $\beta$ , which hydrolysed gives strophanthidin together with glucose and cymarose,\*  $C_7H_{14}O_4$ .

Uzarine on hydrolysis gives  $\alpha$ -anhydrouzarigenin and two molecules of glucose.

All the genins have the cyclopentenophenanthrene skeleton characteristic of steroids, and in nearly all cases the rings are completely saturated. There is usually the characteristic OH group in position 3, and usually one or more OH groups together with methyl groups in 10 and 13, and occasionally a  $\cdot$ CHO in place of Me at 10. The characteristic group of the genins appears to be a lactone ring in position 17, viz.

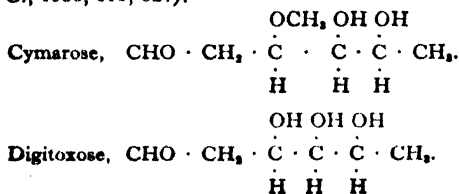
$\cdot\text{C} \begin{array}{l} \nearrow \text{CH}_2\cdot\text{CO} \\ \searrow \text{CH}\cdot\text{O} \end{array}$ , which can be oxidized to  $\cdot\text{CO}_2\text{H}$ . It is a lactone

derived from a  $\beta\gamma$ -unsaturated acid with an OH group  $\alpha$  to the double link  $\text{OH}\cdot\text{CH}:\text{C}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OH}$ . This is proved by the fact that all give Legal's reaction, viz. a pyridine solution of the genin, and sodium nitroprusside gives a deep red colour on the addition of a few drops of alkali. This reaction is specific and is not given by other lactones. Lactones of this type undergo fission on reduction unless the  $\beta$ -carbon atom carries a substituent, and as the lactone ring of the genins is not ruptured on reduction the conclusion is drawn that this ring is attached to the pentenophenanthrene skeleton by its  $\beta$ -carbon atom.

The commoner heart poisons are:

1. **Digitoxigenin**,  $C_{23}H_{34}O_4$ , with OH at 3 and 14, Me at 10 and 13, and the lactone ring at 17 (cf. formula opposite p. 1101).

\* The sugars cymarose,  $C_7H_{14}O_4$ , digitoxose,  $C_6H_{12}O_4$ , and digitalose have not been met with in other plants and are represented as follows (*Eldersfelt*, J. Biol. C., 1935, 111, 827):



2. **Digoxigenin**,  $C_{23}H_{34}O_5$ , also from digitalis, has three OH groups at 3, 11 and 13.

3. **Gitoxigenin**,  $C_{23}H_{34}O_5$ , similar to 1, but with a third OH at 16.

4. **Strophanthidin**,  $C_{23}H_{32}O_6$ , with OH at 3, 5 and 14, CHO at 10, Me at 13, and the lactone ring at 17.

5. **Uzariogenin**,  $C_{23}H_{34}O_5$ , isomeric with 3, and has the three OH groups at 3, 8 and 14.

6. **Periplogenin**,  $C_{23}H_{34}O_5$ , with the three OH groups at 3, 5 and 14.

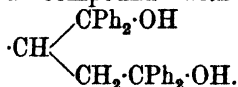
7. **Sarmentogenin**,  $C_{23}H_{34}O_5$ , stereoisomeric with 2 with respect to C atom No. 9.

The presence of the cyclopentenophenanthrene skeleton in these compounds was demonstrated by *Tschesche*, who converted uzariogenin by the following series of reactions into the same aetio-*allo*-cholanolic acid as that obtained from cholesterol:

(a) The OH groups are removed and the olefine link in the lactone hydrogenated.

(b) The saturated lactone is oxidized when the dibasic acid group  $\cdot\text{CH} \begin{cases} \text{CO}_2\text{H} \\ \text{CH}_2\text{-CO}_2\text{H} \end{cases}$  in position 17 is obtained.

(c) The methyl ester of this acid with  $\text{PhMgBr}$  gives a compound with the ditertiary alcohol group at 17:



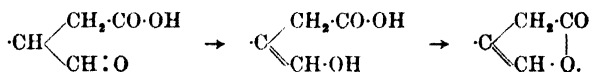
(d) On oxidation this yields benzophenone (2 mols.) and aetio*allo*cholanolic acid, i.e. the monobasic acid with  $\cdot\text{CO}_2\text{H}$  in position 17.

Digitoxigenin treated in the same way gives aetiocholanolic acid, and all cardiac genins give *Diel's* hydrocarbon, methycyclopentenophenanthrene, by selenium dehydrogenation.

The reduction of the olefine link in the lactone, or the opening of the ring, deprives the compounds of their physiological activity. The sugar residues in the original poisons appear to be of value in rendering the genins more soluble and more readily absorbed.

The lactone ring may be regarded as derived from the side chain,  $\cdot\text{CH}(\text{CH}_3)\cdot\text{CH}_2\cdot\text{CO}\cdot\text{OH}$ , present in norcholanolic acid, viz.

oxidation of the  $\text{CH}_3$  to  $\text{CHO}$ , the aldehyde reacting in the enolic form:



Numerous stereoisomerides are possible, due both to *cis* and *trans* fusion of rings and also the normal and epi positions of substituents. Dihydrostrophanthidin is concluded to have a *cis*-decalin fusion of rings A and B, as the cyanohydrin formed by the addition of  $\text{HCN}$ , when hydrolysed, yields a hydroxy acid which forms a lactone with great ease ( $\text{OH}$  from  $\text{CO}_2\text{H}$  and  $\text{H}$  from  $\text{OH}$  at 5), a reaction only possible with a *cis*-fusion of A and B, and it is probable that this *cis*-type of fusion of A and B is characteristic of all the highly active heart poisons of the digitalis group (cf. Rep., 1934, 218; 1936, 363).

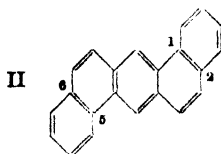
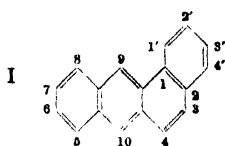
## F. Saponins

The saponins form a group of glycosides widely distributed in the vegetable kingdom. They are soluble in water, insoluble in ether, and give stable emulsions with water and oils. They have a bitter acid taste, give a soapy foam when shaken with water, and have a hæmolytic action on red blood corpuscles yielding hæmoglobin. They form definite compounds with sterols and are used for isolating and estimating these in plant extracts. Thus digitonin and cholesterol give an insoluble compound containing equal molecular proportions. They also form definite additive compounds with such compounds as phenols, thiophenols, ethers, ketones and terpineol. On hydrolysis they yield sugars and genins, the *sapogenins*. Soapwort (*Saponaria officinalis*) root contains saporubin, but those which have been most carefully examined are derived from species of digitalis. Sarsaparilla root yields the genin sarsasapogenin,  $\text{C}_{27}\text{H}_{44}\text{O}_3$ , stereoisomeric with tigenin.

*Digitalis purpurea* contains, in addition to the cardiac glycosides (this Chap., E.), three saponins (given below) which on hydrolysis give the corresponding genin and a mixture of



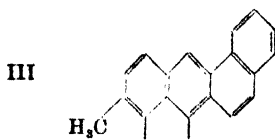
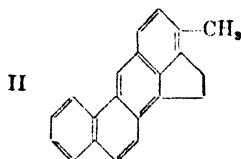
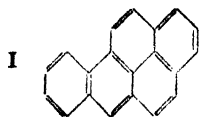
these properties to any appreciable extent was 1:2:5:6 dibenzanthracene II, a derivative of 1:2-benzanthracene I.



This hydrocarbon readily produces skin cancer on mice when they are painted twice weekly with a 0.3 per cent solution.

Cook and his co-workers have investigated a number of complex hydrocarbons and draw the conclusion that derivatives of 1:2-benzanthracene with alkyl substituents in positions 5 and 6, or a 5- or 6-membered C ring fixed in this position, have carcinogenic properties. Of the two the five position appears to have a higher value than the 6. Substituents or rings attached in other positions to the 1:2-benzanthracene molecule, e.g. in 2':3', 3':4', 3:4, 6:7, or 7:8 produce no carcinogenic activity. The addition of further rings (5- or 6-membered) to 1:2:5:6-dibenzanthracene diminishes its activity.

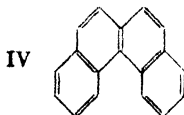
Compounds showing great activity are benzpyrene (Formula IX, Chap. XXXII, C.), which may be written as I and is then seen to be a derivative of 1:2-benzanthracene, also methyl cholanthrene II (Synthesis, J. A. C. S., 1936, 2482), which when written in the form III is seen to be a 5:6:10-substituted 1:2-benzanthracene, and can be obtained from desoxycholic acid (this Chap., B.) or by synthesis (J. A. C. S., 1935, 228, 942).



Cholanthrene and 5:10-dialkyl derivatives of 1:2-benzanthracene appear to be equally active, and the presence of the fifth ring in cholanthrene is not essential. The introduction of substituents in positions other than 5 and 10 lessens the activity.

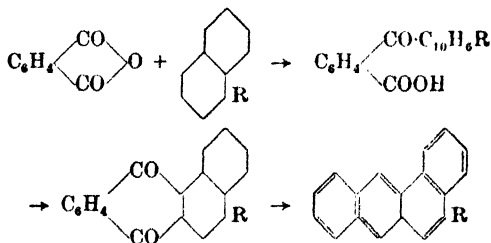
Both 1:2:5:6-dibenzacridine and its 3:4:5:6-isomer have feeble carcinogenic properties.

Only a few compounds which cannot be regarded as related to 1:2:5:6-dibenzanthracene have the power of producing cancer; of these 3:4-benzphenanthrene IV, *s*-triphenylbenzene and tetraphenylmethane are noticeable.



Of the synthetical methods used in the preparation of some of these complex systems the following are of interest.

1. **Phthalic Anhydride Synthesis**, analogous to *Haworth's* phthalic anhydride synthesis of phenanthrene derivatives (Chap. XXXII, B.).—The condensation with a naphthalene derivative, with aluminium chloride as catalyst, gives a ketonic monobasic acid, which, in the presence of sulphuric acid, undergoes ring closure yielding a quinone which can be reduced by zinc and ammonia to a 1:2-benzanthracene derivative.



In certain cases the carbonyl group renders the ring closing very slow, and it is then advisable to reduce the CO to

CH<sub>2</sub> before ring closure so that the system  $\text{C}_6\text{H}_4 \begin{array}{c} \text{CH}_2 \\ \diagup \quad \diagdown \\ \text{CO} \end{array} \text{C}_{10}\text{H}_5\text{R}$

is formed, which can then be reduced to the hydrocarbon. When alkylated naphthalenes are used, migration of alkyl groups can occur, so that arguments as to structure based upon

this method of synthesis must be accepted with reserve. In other cases molecular rearrangements occur, so that in place of the 1 : 2 : 7 : 8-dibenz compound expected, the 1 : 2 : 5 : 6-isomer is formed (*Cook and others, J. C. S., 1932, 1472, 3742; 1933, 3342*).

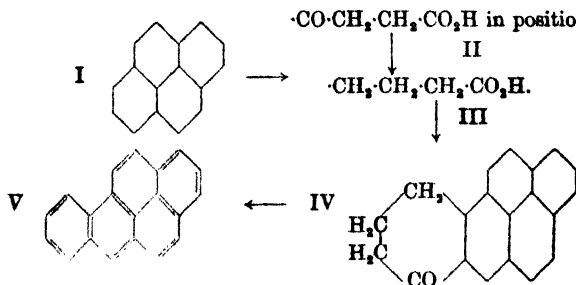
By using naphthalene-1 : 2-dicarboxylic acid anhydride and a benzene derivative various substituted benzantracenes can be obtained, e.g. the 6- and 7-*iso*-propyl compounds.

By using  $\alpha$ -naphthoyl chloride and  $\beta$ -methylnaphthalene and reducing the ketonic acid before cyclization, 1 : 2 : 7 : 8-dibenzanthracene is obtained by condensing, oxidizing the methyl group with selenious acid, reducing, ring closure, and final reduction.

**2. Pschorr Synthesis.**—1 : 2 : 5 : 6-Dibenzanthracene was first synthesized by this method (*M., 1918, 315*).

The procedure is analogous to that described in Chap. XXXII, B., but the sodium salt of a dibasic acid, e.g. *p*-phenylenediacetic acid,  $C_6H_4(CH_2 \cdot CO_2H)_2$ , and two molecules of the aldehyde, *o*-nitrobenzaldehyde are used. By elimination of two molecules of carbon dioxide from the final dibasic acids a mixture of 1 : 2 : 5 : 6- and 3 : 4 : 5 : 6-dibenzanthracenes is formed, but the yields are not good. The method has been used for synthesizing 3 : 4-benzphenanthrene from *o*-nitrobenzaldehyde and naphthalene- $\beta$ -acetic acid,  $C_{10}H_7 \cdot CH_2 \cdot CO_2H$  (*J. C. S., 1931, 2524*).

**3. Succinic Anhydride Synthesis** (cf. Chap. XXXII, B.).—1 : 2-benzpyrene is formed by condensing pyrene I with succinic anhydride, reducing the ketonic acid II with zinc to III, ring closure with stannous chloride to the tetrahydrocyclo compound IV, followed by reduction with selenium or zinc to benzpyrene V :



Cf. *J. C. S., 1933, 400, and B., 1935, 1079.*

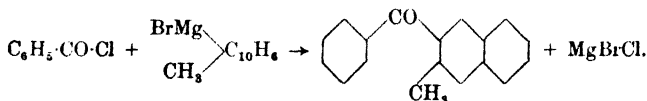


**4. Elbs' Synthesis.**—The conversion of *o*-tolylphenylketone into anthracene (Chap. XXXII, A.) by pyrolysis is the basis of a general method for the syntheses of substituted anthracenes worked out by *Elbs* (B., 1884, 2847; 1885, 1797; 1886, 408; J. pr., 1886, **33**, 180; 1887, **35**, 465; **41**, 1, 121). This method was extended by *Clar* (B., 1929, 350, 1378, 1827) to naphthyl ketones with an *ortho* methyl substituent.

To obtain these *o*-methyl ketones the following methods may be used:

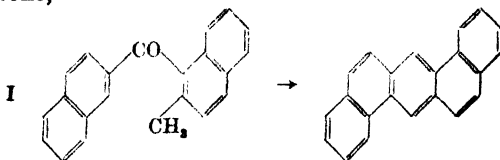
(a) Condensation by the *Friedel-Crafts* method of aroyl chlorides with  $\beta$ -methylnaphthalene.

(b) Reaction between an aroyl chloride and the *Grignard* compound obtained from bromo-2-methylnaphthalene:



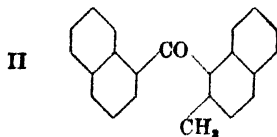
On heating to about 400° the ketones lose water and yield polycyclic hydrocarbons.

Thus  $\beta$ -naphthoyl chloride and  $\beta$ -methylnaphthalene yield the ketone,



which on pyrolysis gives 1:2:5:6-dibenzanthracene. The yield is 32 per cent, and it is the best method of preparing the compound, a by-product is the isomeric 1:2:6:7-dibenzanthracene.

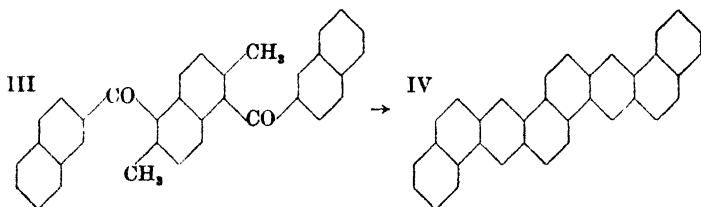
Caution must be exercised in deducing structures from this method of synthesis as (a) several isomers may be formed; and (b) molecular rearrangement may occur during the synthesis, e.g. the ketone (II, isomeric with I) gives 1:2:5:6- and



not 1:2:7:8-dibenzanthracene, due to the wandering of the methyl- $\alpha$ -naphthoyl group for 1' to 2'' position; (c) methyl groups may be eliminated during the reaction as high temperatures are used, and even an isopropyl group may be degraded to a methyl group.

The structure of the final products can, however, usually be established by examination of oxidation products, e.g. the particular anthraquinone poly-carboxylic acids formed on oxidation with permanganate.

An extension of *Elbs'* synthesis to diketones gives rise to still more complex hydrocarbons (*Fieser* and *Dietz*, B., 1929, 1827). Thus the diketone (III) from 2:6-dimethylnaphthalene and two molecules of  $\beta$ -naphthoyl chloride gives as final product 2:3:8:9-di-(1':2' naphtho) chrysene (IV) (52 per cent yield).



Compare B., 1929, 950; J. A. C. S., 1935, 228, 942.

#### LXIV. NATURAL COLOURING MATTERS

Several important colouring matters which occur naturally, e.g. indigo and alizarin, have been referred to in earlier chapters. The compounds dealt with in this chapter fall into four important groups:

- A. Carotenoids.
- B. Flavones and Isoflavones.
- C. Anthocyanins.
- D. Porphyrin Group.

## A. Carotenoids \*

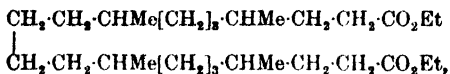
## 1. HYDROCARBONS

The natural yellow colouring matters, the carotenes,  $C_{40}H_{56}$ ; the hydroxylic xanthophylls, e.g. lutein  $C_{40}H_{56}O_2$ , and similar compounds containing a long chain of alternate double and single carbon linkings, i.e. **polyenes**, with or without  $\alpha$ - or  $\beta$ -ionone terminal rings are called carotenoids. Simple members of the group are bixin, crocetin, &c.

**Bixin**,  $C_{25}H_{30}O_4$ , one of the colouring matters of annatto (*Bixa orellana*), has m.-pt.  $196^\circ$ . Its chief reactions (Helv., 1930, 1084; 1931, 435) are: (1) It contains a free carboxyl group and gives esters in the usual manner. (2) It contains a  $\cdot CO_2Me$  group and on hydrolysis yields norbixin, a dibasic acid. (3) When hydrogenated with hydrogen and palladium it takes up 18 atoms of H, indicating the presence of 9 olefine linkages, presumably all conjugate. (4) When oxidized it gives 4 molecules of acetic acid and oxalic acid.

Perhydronorbixin, obtained by hydrogenation of bixin with palladinized barium sulphate and subsequent hydrolysis, has been synthesized by the following method (Helv., 1932, 1218):

Diethyl  $\alpha\alpha'$ -dimethylpymelate,  $CO_2Et\cdot CHMe\cdot [CH_2]_3\cdot CHMe\cdot CO_2Et$ , obtained from trimethylene bromide and ethyl sodium-methylmalonate, on reduction gives 2:6-dimethylheptane-1:7-diol,  $OH\cdot CH_2\cdot CHMe\cdot [CH_2]_3\cdot CHMe\cdot CH_2\cdot OH$ , and the corresponding 1:7-dibromide condenses with ethyl sodium-malonate, giving diethyl 3:7-dimethylnonane-1:9-dicarboxylate,  $CO_2Et\cdot CH_2\cdot CH_2\cdot CHMe\cdot [CH_2]_3\cdot CHMe\cdot CH_2\cdot CH_2\cdot CO_2Et$ . On partial hydrolysis this yields the sodium salt of the acid ester, which on electrolysis yields the diethyl ester of perhydronorbixin,

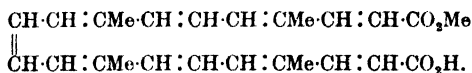


and on hydrolysis perhydronorbixin identical with the product obtained from bixin.

This synthesis indicates the positions of the carboxylic and methyl groups in bixin, and also proves that it contains a

\* Carotenoide, L. Zechmeister, Berlin, 1934. For Summary, cf. *Spring, Rep.*, 1935, 291.

normal chain of carbon atoms. Bixin with 9 olefine linkings presumably conjugate is therefore

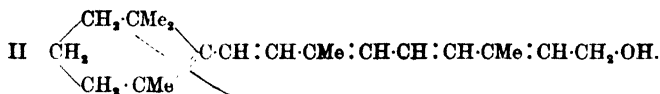


Under certain conditions ordinary bixin yields an isomeride,  $\beta$ -bixin, melting at  $270^\circ$ , and the two are regarded as *cis* and *trans* stereoisomerides as both yield the same dihydro derivative.

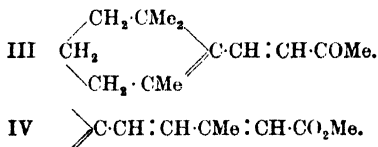
**Crocetin**,  $\text{C}_{30}\text{H}_{24}\text{O}_4$ , a yellow pigment from saffron (*Crocus sativus*), melts at  $285^\circ$ , and is a dibasic acid with four methyl groups and with 7 olefine linkages presumably conjugate. Its perhydro derivative has been synthesized in much the same manner as perhydronorbixin (Helv., 1933, 297), starting with 2:6-dimethyl-heptandiol-1:7,  $\text{OH}\cdot\text{CH}_2\cdot\text{CHMe}[\text{CH}_2]_3\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{OH}$ , which is converted into the monoethyl ether and then into the monobromide  $\text{Br}\cdot\text{CH}_2\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{OEt}$ . This with ethyl sodiomalonate gives  $(\text{CO}_2\text{Et})_2\text{CH}\cdot\text{CH}_2\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{OEt}$ , which on hydrolysis and loss of carbon dioxide gives the monobasic acid, 4:8-dimethyl-9-ethoxy-nononic acid,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{OEt}$ , and on electrolysis the sodium salt gives 2:6:11:15-tetramethyl-1:16-diethoxyhexadecane,  $[\text{OEt}\cdot\text{CH}_2\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CH}_2]_2$ . With hydrobromic acid the OEt groups are replaced by Br, and these by OH by means of potassium acetate and subsequent hydrolysis, and the resulting diprimary alcohol on oxidation with chromic acid gives the dibasic acid  $[\text{CO}_2\text{H}\cdot\text{CHMe}[\text{CH}_2]_3\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{CH}_2]_2$  identical with perhydrocrocetin. Crocetin is therefore  $\text{CO}_2\text{H}\cdot\text{CMe}:\text{CH}\cdot\text{CH}:\text{CH}\cdot\text{CMe}:\text{CH}\cdot\text{CH}:\text{CH}\cdot\text{CH}:\text{CMe}\cdot\text{CH}:\text{CH}\cdot\text{CH}:\text{CMe}\cdot\text{CO}_2\text{H}$ , and this formula has been confirmed by its direct synthesis (Helv., 1934, 545). An isomeric crocetin also present in saffron melts at  $141^\circ$  and is probably the *cis* form of ordinary crocetin.

**Vitamin A** has so far been obtained as a pale yellow oil, b.-pt.  $137^\circ$ – $138^\circ$ , under extremely low pressures. It is unsaturated, contains 5 olefine linkings conjugate, is a primary alcohol, and on oxidation gives geronic acid I (1 mol.) and acetic acid (3 mols.). The structure II, based on these reactions,

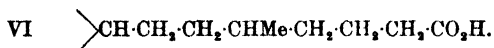
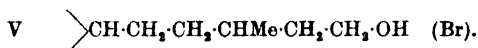




has been confirmed by the synthesis of its perhydro derivative as follows:  $\beta$ -ionone III (Chap. LVII, E.) with methyl bromoacetate and zinc (*Reformatsky* reaction) and subsequent elimination of water yields IV,



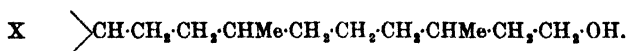
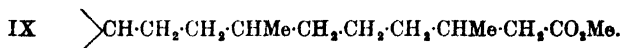
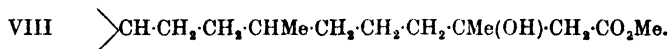
which on hydrogenation and subsequent reduction with sodium and alcohol gives V, and the corresponding bromide



with ethyl sodiomalonate and subsequent hydrolysis yields VI, the acid chloride of which with zinc and methyl iodide gives VII.



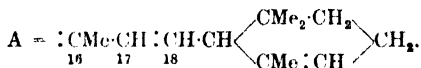
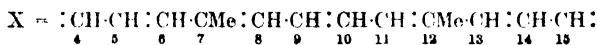
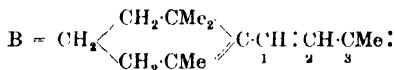
This condensed with zinc and methyl bromoacetate gives VIII, and by replacing OH by Br and reduction gives IX, and on final reduction with sodium and alcohol X,



which is identical with the perhydro derivative of natural vitamin A as proved by conversion into crystalline compounds with definite melting-points.

**Carotenes.**—The yellow colouring matter carotene, from carrots, palm oil, spinach, nettles, &c., has been shown to be a mixture of at least three closely related compounds— $\alpha$ -,  $\beta$ -, and  $\gamma$ -carotenes,  $C_{40}H_{56}$ . These can be separated by a process of adsorption (*Tswell's* method of chromatographic analysis). When a light petroleum solution of the colouring matter is filtered through calcium hydroxide or lime the  $\beta$ -compound is adsorbed in the dark brown upper layer, and the  $\alpha$ -carotene in the yellow lower layer, and the  $\gamma$ -compound can be adsorbed by aluminium hydroxide (cf. *Heilbron*, J. S. C. I., 1937, 160 T.).

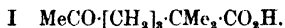
**$\beta$ -Carotene**, which is optically inactive and melts at  $183^\circ$ , is given the symmetrical formula B : X : B by *Karrer*, where B represents a residue with a terminal  $\beta$ -ionone group,



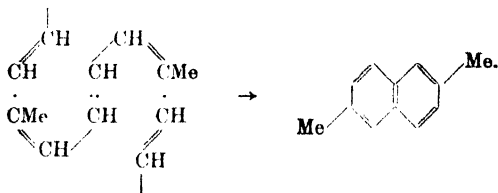
and X the polyene chain with two methyl substituents. Oxidation with chromic acid gives a dihydroxy compound derived from the  $\beta$ -ionone portion of the molecule by the addition of two OH groups to the olefine link, together with a diketone,  $\beta$ -semicarotenone, formed by the opening of the ring at the olefine link, and also  $\beta$ -carotenone, a tetraketone formed in the same way from the second ionone group. These products on further oxidation yield  $\beta$ -carotenone aldehyde,  $C_{27}H_{36}O_3$ , which has the structure  $\text{MeCO}[\text{CH}_2]_3 \cdot \text{CMe}_2 \cdot \text{CO} \cdot \text{CH} : \text{CH} \cdot \text{CMe} : \text{CH} \cdot \text{CH} : \text{CH} \cdot \text{CMe} : \text{CH} \cdot \text{CH} : \text{CH} \cdot \text{CH} : \text{CMe} \cdot \text{CH} : \text{CH} \cdot \text{CHO}$ . Only one product is formed, hence the polyene chain is symmetrical and the two terminal rings are identical, and the fission of the polyene chain in the last oxidation occurs between carbons 3 and 4 and 15 and 16.

The formation of 4 molecules of acetic acid from one of the aldehyde by drastic oxidation indicates the presence of 3 Me groups, as the fourth molecule is formed from the terminal  $\text{CO} \cdot \text{CH}_3$  group. The symmetrical formula is also supported

by the fact that on ozonolysis the hydrocarbon yields geronic acid I but no isogeronic acid II:

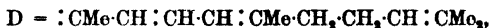


Careful thermal degradation of  $\beta$ -carotene gives 2:6-dimethylnaphthalene by the cyclization of the 10 middle C atoms of the polyene chain, thus indicating the positions of the two methyl groups:



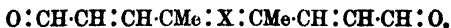
$\alpha$ -Carotene is optically active, has m.-pt.  $187^\circ$ , and contains 11 double linkings. On ozonization it gives equal quantities of geronic and isogeronic acids, and hence has a terminal  $\beta$ - and a terminal  $\alpha$ -ionone group, and is represented by the formula B : X : A (*Karrer* and others, *Helv.*, 1933, 975).

$\gamma$ -Carotene is optically inactive, has m.-pt.  $178^\circ$ , and gives absorption bands intermediate between those of  $\beta$ -carotene and lycopene, and as it contains 12 olefine linkings as compared with 11 in  $\beta$ -carotene and 13 in lycopene it is represented as B : X : D, where



i.e. one of the terminal rings has opened. The amount of the  $\gamma$ -compound present is very small compared with the isomerides.

**Lycopene**,  $\text{C}_{40}\text{H}_{56}$ , isomeric with the carotenes, is the colouring matter of bitter-sweet berries, tomatoes and rose hips. It contains no terminal rings but 13 olefine linkings, and has an absorption quite different from those of  $\alpha$ - and  $\beta$ -carotenes. It is represented as D : X : D, and this structure has been confirmed by oxidation to 2-methyl- $\Delta^2$ -hepten-6-one,  $\text{CMe}_2 \cdot \text{CH}[\text{CH}_2]_2 \text{CO} \cdot \text{Me}$ , and lycopenal,  $\text{O} : \text{CH} \cdot \text{CH} : \text{CH} \cdot \text{CMe} : \text{X} : \text{D}$ , and this latter on further oxidation yields bixindialdehyde,



and methylheptenol.

All three carotenes have qualitatively the same physiological action on rats deficient in vitamin A, but quantitatively the  $\beta$ -compound is twice as active as  $\alpha$  or  $\gamma$ , and this is probably due to the fact that the  $\beta$ -molecule can give rise to two molecules of vitamin A, whereas the  $\alpha$ - and  $\gamma$ -compounds can give only 1 molecule. Lycopene is physiologically inactive. The structure of vitamin A is similar to that of the left half of carotene  $\beta$  but with the  $\cdot\text{CH}_2\cdot\text{OH}$  group in position 5.

Activity is due to the presence of the  $\beta$ -ionone ring, thus semi- $\beta$ -carotenone (p. 1137) is physiologically active, but  $\beta$ -carotenone is not.

## 2. HYDROXY COMPOUNDS

**Xanthophylls** are hydroxy derivatives of the carotenes. A better generic name is **phytoxanthins**, and the name xanthophyll is then restricted to a particular dihydroxycarotene. Many of the phytoxanthins occur in plants in the form of esters of fatty acids. The commoner phytoxanthins are:

**Kryptoxanthenin**,  $\text{C}_{40}\text{H}_{55}\cdot\text{OH}$ , occurs as an ester in the red berries of species of *Physalis*, and is probably a  $p$ -hydroxy- $\beta$ -carotene; **zeaxanthin**,  $\text{C}_{40}\text{H}_{54}(\text{OH})_2$ , from the ripe fruits of the yew and from yellow maize, is in all probability a  $pp'$ -dihydroxy- $\beta$ -carotene; **lutein** or **xanthophyll**, from egg-yolk and green leaves, is the corresponding derivative of  $\alpha$ -carotene.

**Capxanthin**, from red pepper, has the structure



**Fucoxanthin** has a symmetrical formula with X attached to two residues:



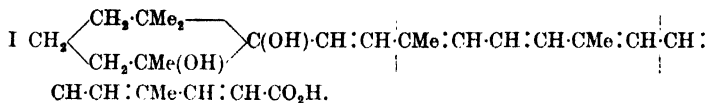
**Astacene**,  $\text{C}_{40}\text{H}_{48}\text{O}_4$ , the characteristic pigment of the *Crustaceæ*, contains 13 olefine linkings, but two of these are due to enolization of the carbonyl groups, as perhydroastacene contains two reactive H atoms and is in all probability a 4:5:4':5'-tetraketo- $\beta$ -carotene.\* It possesses acidic properties due to enolization.

**Azafrin**,  $\text{C}_{37}\text{H}_{38}\text{O}_4$ , obtained from azafrin roots, is optically

\* The numbers refer to the positions of the carbonyl groups in the two terminal rings.



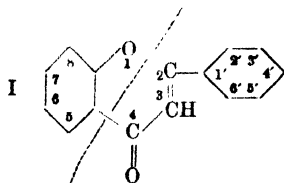
active, contains seven conjugate double linkings, and contains two tertiary alcohol groups and one carboxylic, and on oxidation gives geronic acid, *m*-xylene and *m*-toluic acids, and is represented as I, the dotted lines indicating the points of fission.



**Capsanthin**, from Paprika (*Capsicum annum*), has at one end a keto group, viz.  $\text{CH}_2\text{Me} \cdot \text{CH}_2 \cdot \text{CH}(\text{OH}) \cdot \text{CH}_2 \cdot \text{CMe}_2 \cdot \text{CO}$ , in place of a terminal ring, and at the other end it has the ring B and a series of alternate single and double bonds in the chain.

## B. Flavones and *iso*-Flavones

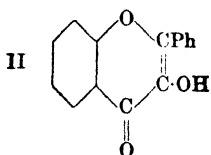
**Flavone**,  $\text{C}_{15}\text{H}_{10}\text{O}_2$ , 2-phenylbenzopyrone, 2-phenylchromone I (cf. Chap. XLIV, A1), is the parent substance of a number of vegetable colouring matters; all of these are polyhydroxy or



methoxy derivatives of flavone and occur in plant tissues as glycosides. Some of the more important of these dyes are glycosides of

Chrysin	..	..	5:7-dihydroxy-flavone.
Primetin	..	..	5:8-dihydroxy-flavone.
Baiculein	..	..	5:6:7-trihydroxy-flavone.
Wogonin	..	..	5:7-dihydroxy-8-methoxy-flavone.
Apigenin	..	..	5:7:4-trihydroxy-flavone.
Acacetin	..	..	5:7-dihydroxy-4'-methoxy-flavone.
Luteolin	..	..	5:7:3':4'-tetrahydroxy-flavone.
Hesperetin	..	..	5:7:3'-trihydroxy-4'-methoxy-flavone.

Many natural products are glycosides of 3-hydroxy flavone II with two or more hydroxyl groups in the benzene ring.



They are known as **flavonols**, and some of the commoner ones are:

Datiscetin .. .. .	5:7:2'-trihydroxy-flavonol.
Kaempferol .. .. .	5:7:4'-trihydroxy-flavonol.
Fisetin .. .. .	7:3':4'-trihydroxy-flavonol.
*Quercetin .. .. .	5:7:3':4'-tetrahydroxy-flavonol.
Morin .. .. .	5:7:2':4'-tetrahydroxy-flavonol.
Myricetin .. .. .	5:7:3':4':5'-pentahydroxy-flavonol.
Gossypetin .. .. .	5:7:8:3':4'-pentahydroxy-flavonol.
Quercetagenin .. .. .	5:6:7:3':4'-pentahydroxy-flavonol.

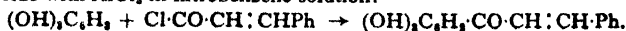
The structure of any flavone derivative is ascertained by:

1. The examination of the products formed by the action of alcoholic potash on the compound, or, more readily, by aspirating air through the dilute alkaline solution. Thus luteolin yields protocatechuic acid (3:4-dihydroxy-benzoic acid (Chap. XXVI, A3) and phoroglucinol, fission of the molecule occurring at the dotted line in I (p. 1140).

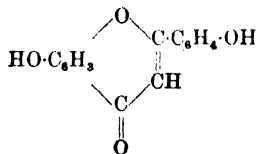
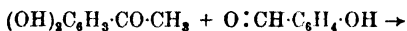
2. Synthesis. (a) A general method for synthesizing flavones is the condensation of benzaldehyde, or an alkyloxy derivative, with hydroxylated acetophenones in the presence of alcoholic potash; the first product is an unsaturated hydroxy-ketone, a **chalcone** † and the dibromide of the acetyl derivative with caustic potash yield a hydroxy-flavone—thus resacetophenone (2:4-dihydroxyacetophenone) and *m*-hydroxybenzaldehyde yield 2:4-dihydroxyphenyl-3-hydroxystyryl ketone, and

\* Catechin is similar to quercetin, but no olefine bond and CH<sub>3</sub> in place of CO.

† Chalcones are also formed from polyhydroxyphenols and cinnamoyl chloride with AlCl<sub>3</sub> in nitrobenzene solution:



finally 7 : 3'-dihydroxyflavone (*Tambor*, B., 1916, 1704; *Helv.*, 1919, 101).

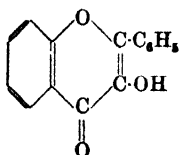


(b) Another general method used by *Robinson* and others (*J. C. S.*, 1925, 181, 1973; 1926, 2336, 2344, 2713; 1928, 1022, 3115; 1929, 61, 74, 152) is to condense a hydroxylated acetophenone, e.g. resacetophenone, phloracetophenone (3OH = 2 : 4 : 6), gallacetophenone (3OH = 2 : 3 : 4), and certain methoxy derivatives with sodium benzoate and benzoic anhydride, or the salt and anhydride of a suitably substituted benzoic acid, and hydrolysing the resulting aroyl derivative. As the positions of the OH groups in the reagents are known, the positions of the OH groups in the flavone follow. A typical example is the condensation of anisic anhydride, sodium anisate and resacetophenone; the product is 7-hydroxy-4-methoxy-flavone identical with **pratol**, the flavone derived from the colouring matter of *Trifolium pratense*.

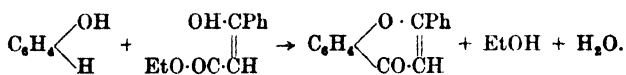
In this reaction no aroyl group enters the 3-position of the pyrone ring; in this respect it differs from the synthesis of chromones using hydroxyacetophenones, acetic anhydride and sodium acetate when an acetyl becomes attached to carbon No. 3 (Chap. XLIV, A1).

When *Robinson's* method is slightly modified by using an  $\omega$ -methoxy derivative of the hydroxyacetophenone, e.g.  $\text{OMe-CH}_2\text{-CO-C}_6\text{H}_3(\text{OH})_2$ , the product contains a methoxy group in position 3, and on demethylation with hydriodic acid a flavone derivative with an OH in position 3, i.e. a **flavonol**. The majority of those mentioned on p. 1141 have been synthesized by this method. A better method is to use the  $\omega$ -benzoyloxy derivative of the ketone, as the resulting

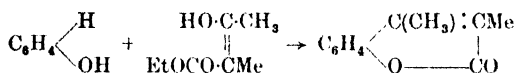
3-benzoyloxy-flavones are much more readily hydrolysed than the methoxy compounds.



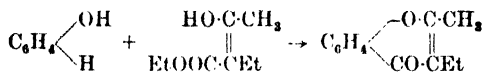
(c) Flavone can be obtained from phenol and the sodium derivative of ethyl benzoylacetate with phosphoric anhydride (*Simonis*) or sulphuric acid (*Pechmann*).



When the nitrile (in place of ester) is used the product is the imine,  $>\text{C}:\text{NH}$ , corresponding with flavone and readily yields the latter with 20 per cent sulphuric acid (*Ghosh*, J. C. S., 1916, 105). The general reaction between phenols and substituted acetoacetic esters,  $\text{CH}_3 \cdot \text{CO} \cdot \text{CHR} \cdot \text{CO}_2\text{Et}$ , has been studied in detail. When  $\text{R} = \text{H}$  or  $\text{CH}_3$  coumarin derivatives are formed:



but when  $\text{R} = \text{Et}$ ,  $\text{Ph}$ ,  $\text{CH}_2\text{Ph}$ , &c., the product is a substituted chromone (*Jacobson* and *Ghosh*, J. C. S., 1915, 424, 959, 1051). *Auwers* and *Anschutz* (B., 1921, 1543) show how a flavone or a coumaranone can be obtained from the same chalcone according to conditions.



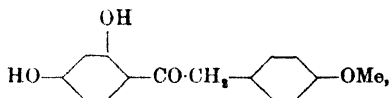
With  $\text{P}_2\text{O}_5$  the product is chiefly a flavone, but with sulphuric acid a coumarin. The type of phenol also affects the reaction; thus the presence of  $\text{Cl}$  or  $\text{NO}_2$  groups in cresols decreases the activity in the *Pechmann* but increases it in the *Simonis* condensation (C. and I., 1936, 619).

In many cases it is advisable to use the nitrile instead of the ester, e.g. acetylphenylacetone nitrile (in its enolic form)



The flavanones obtained from natural glycosides are optically inactive, probably due to racemization during preparation, but can be resolved by means of *l*-methoxy-acetyl chloride (J. A. C. S., 1934, 2109).

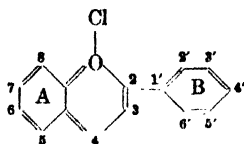
**The position of the sugar residue in natural flavone derivatives.**—The general method, which is used also in the case of many other glycosides (cf. Chap. LVI, F.), is completely to methylate the glycoside and then examine the products of alkaline fission. One of these will be the methylated glucose (or other sugar), and the other a methoxy-dihydroxy-phenyl benzyl ketone or its decomposition products. Of the two hydroxy groups, one, i.e. *ortho* to CO group, is derived from the O of the flavone ring, and the other from the —O·Sugar group. Thus from daidzein (7 : 4'-dihydroxy-isoflavone) the final products are methylglucose and 2 : 4-dihydroxy-phenyl-*p*-methoxybenzyl ketone,



proving that the sugar group was attached to OH in 7 and not in the 4'-position. (For numbering see formula, p. 1140.)

### C. Anthocyanins

Many of the vivid colouring matters of plants, especially flowers, have been studied in detail, first by *Willstätter* and *Everest* and later by *Robinson* and his co-workers. They are termed **anthocyanins**, and are mono- or di-glycosides\* derived from hydroxylated or methoxylated bases closely related to flavone. When hydrolysed with hydrochloric acid they yield the sugar or sugars and the chloride of the sugar free base, the **anthocyanidin** or **flavylium** chloride.†



\* Used in the generic sense as sugars other than glucose are involved.

† Just as the corresponding salts from pyrones are called pyrylium and from chromone chromylium salts.

Their close relationship to flavanols is shown by the fact that quercitin with magnesium and hydrochloric acid yields cyanidine chloride.

The simplest—unsubstituted—flavylium chloride is represented by *Robinson* as having an orthoquinonoid structure shown above, and the compounds derived from the natural anthocyanins contain hydroxy or methoxy substituents in both rings A and B. Views on the actual structure of the salts have varied from time to time. They were first represented

as oxonium salts  $\begin{array}{c} \text{H} \\ \diagup \\ \text{O} \\ \diagdown \\ \text{Cl} \end{array}$ , then by the *Robinson* orthoquinonoid

structure, and recently there has been a tendency to represent the chlorine as derived from carbon atom 2 or 3 (cf. p. 1150).

The following is a list of some of the commoner flavylium chlorides:

1. Pelargonidin .. 3:5:7:4'-tetrahydroxy-flavylium chloride.
2. Cyanidin .. 3:5:7:3':4'-pentahydroxy-flavylium chloride.
3. Paeonidin .. 3:5:7:4'-tetrahydroxy-3'-methoxy-flavylium chloride.
4. Delphinidin .. 3:5:7:3':4':5'-hexahydroxy-flavylium chloride.
5. Petunidin .. 3:5:7:4':5'-pentahydroxy-3'-methoxy-flavylium chloride.
6. Malvidin .. 3:5:7:4'-tetrahydroxy-3':5'-dimethoxy-flavylium chloride.
7. Hirsutidin .. 3:5:4'-trihydroxy-7:3':5' trimethoxy-flavylium chloride.

The anthocyanins are 3-mono- or 3:5-di-glycosides, all of the  $\beta$ -type, of the above. **Callistephin** is the 3-glucoside of No. 1, and occurs in red asters and scarlet geraniums; **chrysanthemin** is the 3-glucoside of 2, and **idein** the corresponding 3-galactoside, and occurs in the skin of cranberries and in copper-beech leaves; the 3-glucoside of 3 is **oxycoccicyanin**, from the leaves of American cranberries; **oenin**, the corresponding 3-glucoside of 6, is the colouring matter of black grapes and of some primulas. The 3:5-diglucosides of the  $\beta$ -type are some of the commonest plant pigments. **Pelargonin** from red pelargoniums, **cyanin** from blue cornflowers, **paeonin** from red peonies, **delphinin** from *Salvia patens*, **malvin** from certain primulas, and **hirsutin** from *Primula hirsuta* are the 3:5-

diglucosides derived from 1, 2, 3, 4, 6 and 7 respectively, and have all been synthesized.

When hydrolysed the 3-glucosidyl group is removed more readily than the 5, so that by partial hydrolysis it is possible to obtain the 5-monoglucosides of 1 to 7 from the above mentioned diglucosides; thus malvin yields **malvenin** and cyanin yields **cyanenin**.

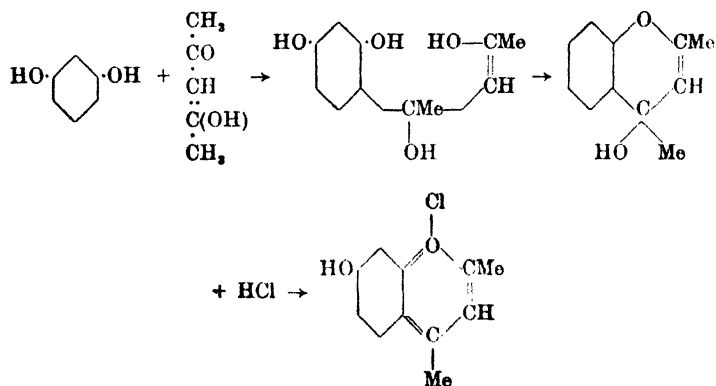
The pigments **mecocyanin**, **prunicyanin**, and **keracyanin** contain a di-saccharide group in position 3.

Acylated anthocyanins also occur in nature, particularly *p*-hydroxy-cinnamoyl compounds; thus **gentianin** and **violanin** are *p*-hydroxy-cinnamates of delphinidin monoglucoside and monorhamnoglycoside respectively.

**Keracyanin** is cyanidin-3-rhamnoglycoside, and **mecocyanin** (from red poppies) is cyanidin-3-gentio-bioside.

### SYNTHESIS OF ANTHOCYANIDINS (FLAVYLIUM SALTS)

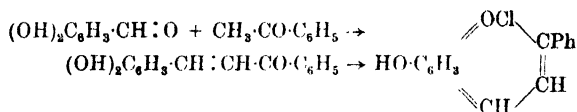
1. *Bulow* obtained the so-called 1:4-benzopyranols by the condensation of reactive phenols with diketones of the type of acetylacetone, reacting in their enolic forms, in the presence of hydrochloric acid:



Using benzoylacetone, the product is a 2-phenyl substituted compound—a flavylium salt.



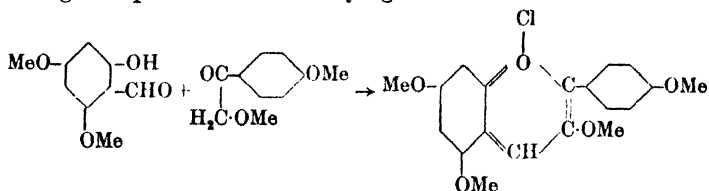
2. *Decker and Fellenberg* (B., 1907, 3815) studied the action of *o*-hydroxybenzaldehydes on ketones,



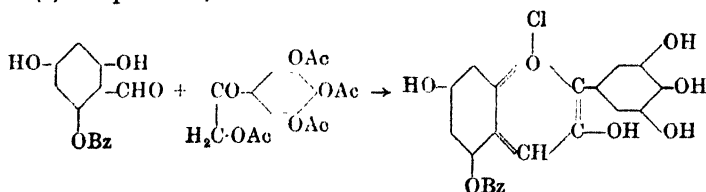
the intermediate product being a chalcone; the method was extended by *Perkin, Robinson and Turner* (J. C. S., 1908, 1085), who deduced the correct structure of the final product, and it is the method now generally used for synthesizing flavylum salts. *Willstätter* (B., 1924, 1938) and *Robinson* and his co-workers (J. C. S., 1924, 188; 1925, 166, 1182) have extended the reaction to the preparation of numerous 3-substituted flavylum compounds, the anthocyanidins, by using  $\omega$ -hydroxyacetophenones and *o*-hydroxybenzaldehydes. As a rule the hydroxyl groups need protection by methylation, acetylation or best benzoylation (1928, 1256). When methyl ethers are used the subsequent demethylation to yield the free hydroxyl compound often yields impure products.

Two typical syntheses are:

(a) Pelargonidin by condensing 2-hydroxy-4:6-dimethoxybenzaldehyde with  $\omega$ :4-dimethoxyacetophenone and demethylating the product and acidifying.



(b) Delphinidin,

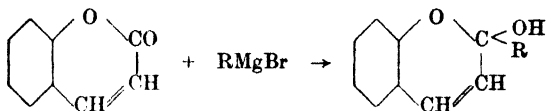


The monobenzoyl ester of phloroglucin-aldehyde is condensed with the fully acetylated 3:4:5: $\omega$ -tetrahydroxy

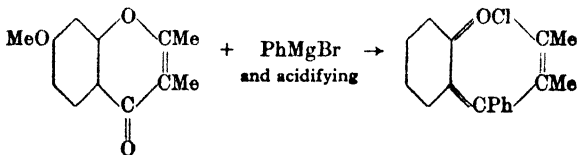
acetophenone with hydrochloric acid when the 5-benzoate of delphinidin chloride is formed, as all acetyl groups are removed during the reaction. On hydrolysis with aqueous alkali the benzoyl group is removed, and on acidifying with hydrochloric acid delphinidin chloride itself is formed.

The intermediate products in these syntheses are the chalcones (this Chap., B.), which undergo ring closure in the presence of acids, and *Pratt and Robinson* (J. C. S., 1922, 1577) have isolated many of these chalcones in a state of purity by using different solvents and have established their identity, and hence the structure of the resulting flavylum salts.

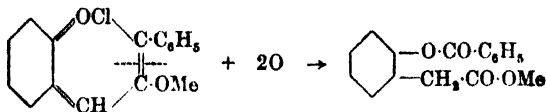
3. A third general synthetical method is the condensation of a *Grignard* compound with a coumarin. *Decker and Fellenberg* (B., 1907, 3815; A., 1907, 356, 281) prepared 2-substituted benzopyrylium salts by this method,



and by using 3-methoxycoumarins *Willstätter* obtained anthocyanidins, and *Heilbronn* and others (J. C. S., 1926, 1902; 1927, 2005; 1931, 1701) have extended the method by obtaining 4-substituted benzopyrylium salts from phenyl magnesium bromide and 2 : 3-dimethyl-7-methoxychromone.



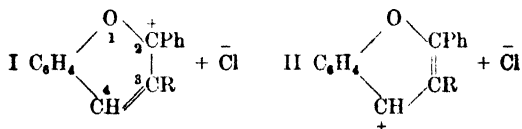
**Structure of Flavylum Salts.**—An interesting confirmation of the structure of the heterocyclic ring is afforded by the oxidation of 3-methoxyflavylum perchlorate with hydrogen peroxide in glacial acetic acid when the *o*-benzoyl derivative of methyl-*o*-hydroxyphenyl acetate is obtained (*Dilthey* and others, B., 1931, 2082; J. pr., 1933, 138, 42).



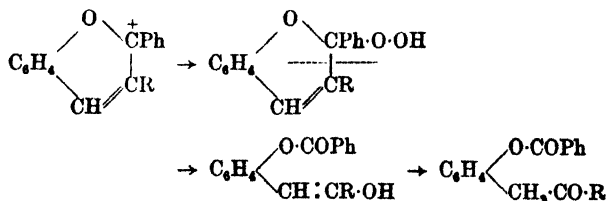
The structure proposed by *Perkin, Robinson and Turner* is of the orthoquinonoid type. The oxygen atom is quadrivalent, and in the ionized salts carries the + charge.

*Le Fevre* (J. C. S., 1929, 2771) found that when flavylum perchlorate is nitrated the product is a *meta* derivative, and hence, presumably, the oxygen atom must be in the same state as in benzaldehyde or acetophenone and cannot therefore be the seat of the + charge.

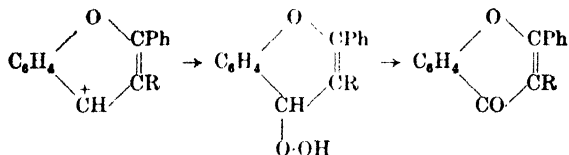
Also the reaction between benzopyrylium salts and *Grignard* reagents (see above; also B., 1924, 1517; J. A. C. S., 1930, 2864) involves a simple interchange between the  $C_6H_5$  of the  $MgC_6H_5Br$  and the anion of the salt, with addition of phenyl sometimes in position 2 and sometimes in position 4, and these facts are not readily explicable on the oxonium theory. Carbonium structures have therefore been suggested by *Dilthey and Quint* (J. pr., 1931, 131, 1; 1933, 138, 42), viz.



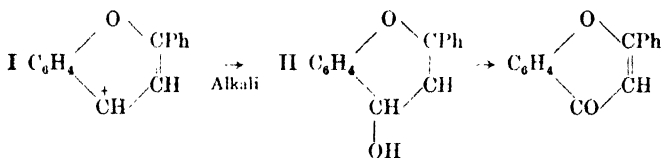
In the one case the + charge is carried by carbon atom No. 2, and in the other by carbon atom No. 4. The majority of the salts probably have structure No. 1, as when oxidized with hydrogen peroxide, the resulting peroxide, which carries the peroxide group attached to the carbon atom carrying the + charge in the salt, is unstable and undergoes a fission of the pyrane ring, yielding the benzoyl ester of an *o*-hydroxybenzyl ketone.



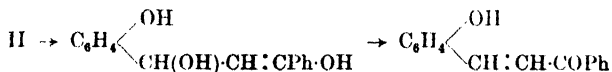
On the other hand, if the charge were carried by the carbon atom No. 4, the flavylum salts when oxidized would yield flavones.



*Hill* and *Meluish* (J. C. S., 1935, 1161) have shown that several flavylum salts not substituted in position 3 can easily be converted into flavones by treatment with sodium carbonate and oxidation, thus supporting the 4-position of the charge,



and appreciable quantities of chalcones are also formed by the decomposition of the pyranol II.

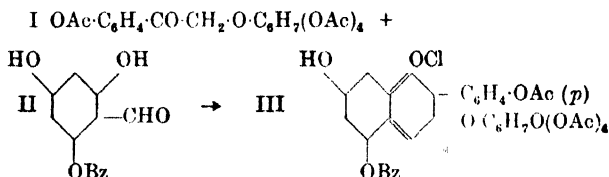


**Syntheses of Anthocyanins.**—Not only have the anthocyanidins been synthesized, but *Robinson* and his co-workers have succeeded in synthesizing the actual colouring matters themselves—the anthocyanins (J. C. S., 1926–32). The method consists in condensing the acetylated glycosidyl derivative of the ketone or aldehyde or of both with hydrogen chloride as in the synthesis for flavylum salts (p. 1147), and it is necessary to protect the hydroxyl group by acetylating or benzoylating. The acetylated glucosidyl group is introduced into the aldehyde or ketone by using the tetracetyl derivative of  $\alpha$ -glucosidyl bromide (acetobromoglucose, p. 341) with dry silver carbonate in benzene.

(a) *Synthesis of callistephin* (3- $\beta$ -monoglucosidyl-pelargonidin chloride).

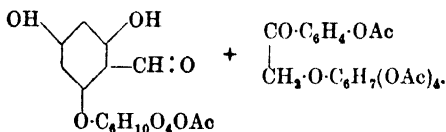
$\omega$ -o-Tetracetyl- $\beta$ -glucosidyl-4-acetoxyacetophenone I, from  $\omega$ -hydroxy-4-acetoxyphenone and acetobromoglucose, condenses with *o*-benzoyl-phloro-glucinaldehyde II in a dry ethereal solution of hydrogen chloride giving III, and this

hydrolysed with 8 per cent sodium hydroxide and subsequent acidification gave the anthocyanin by the elimination of acetyl and benzoyl groups.



(b) *Synthesis of a 3:5-diglucoside*, e.g. pelargonin chloride.

In this case the condensing agents are the *o*-acetylglucosidyl derivative of phloroglucinaldehyde and the acetylglucosidyl ketone used in (a).

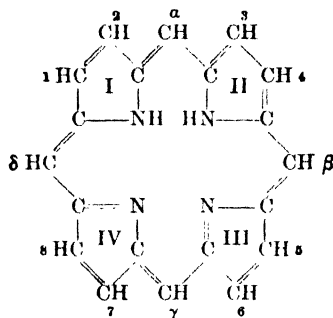


The resulting acetylated condensation product when kept in dilute alkali in an atmosphere of hydrogen loses the acetyl groups and on acidification with hydrochloric acid pelargonin chloride is obtained.

The anthocyanins are amphoteric in character, and the bases yield salts with both acids and alkali, and undergo a great variety of colour changes with variation in the  $p_H$  values of solvents.

Nitrogenous anthocyanins are also known; cf. *Ainley and Robinson*, J. C. S., 1937, 446.

### D. Porphyrin Group \*



The basic units of both the green pigment of plants and the red colouring matter of blood appear to be porphyrins. The simplest unsubstituted porphyrin is represented by the above formula. It is termed **porphin** and has been synthesized by *Hans Fischer* (A., 1935, 521, 157). In structure the porphyrins closely resemble the phthalocyanines (Chap. LIX, L.) with the exception that the  $\text{:CH}$  groups labelled  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$  in the above formula are replaced by  $\text{:N}$ .

Both types of compounds contain a 16-membered ring and are characterized by their stability, and in this respect differ from the pyrrole and *iso*-indole rings from which they may be regarded as built up. In many respects they possess true aromatic properties, e.g. halogenation, nitration, sulphonation and reduction, and appear to form flat or uniplanar rings.

A number of porphyrins have been found in nature, e.g. in minerals, &c.,

		Side Chains
Copro-porphyrin	$\text{C}_{36}\text{H}_{36}\text{O}_8\text{N}_4$	$4\text{CH}_3$ , 4 X
Concho-porphyrin	$\text{C}_{27}\text{H}_{38}\text{O}_{10}\text{N}_4$	$4\text{CH}_3$ , 1 X, 1 succinic acid.
Oo-porphyrin	$\text{C}_{34}\text{H}_{34}\text{O}_6\text{N}_4$	$4\text{CH}_3$ , 2 ethyl, 2 vinyl.
Uro-porphyrin	$\text{C}_{40}\text{H}_{38}\text{O}_{10}\text{N}_4$	$4\text{CH}_3$ , Methyl-malonic and succinic acids.



\* *Linstead*, Rep., 1935, 359.

and some of these have been synthesized, and in addition a large number of other porphyrins have been prepared by *Fischer* (A., 1928-31). The methods adopted were:

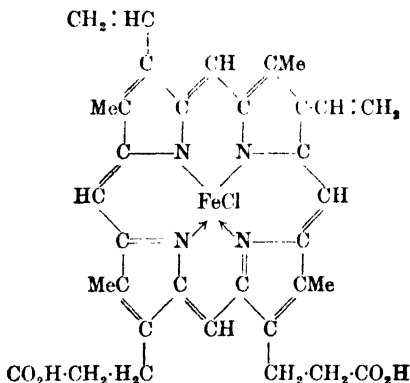
(1) Condensation of 3 : 4-dialkylpyrroles with formaldehyde or formic acid.

(2) By fusion of 2 : 2'-dibromodipyrromethanes with 2 : 2'-dimethyldipyrromethanes in succinic acid.

These synthetic products have proved of inestimable value in elucidating the structure of the porphyrins obtained by the degradation of chlorophyll and hæmin.

### 1. BLOOD PIGMENT \*

**Hæmin**, Haematin hydrochloride,  $C_{34}H_{32}O_4N_4FeCl$ , (Chap. LXVII, A2), has been proved both by degradation and synthesis to be a porphyrin derivative with the following structure, viz. 1 : 3 : 5 : 8-tetramethyl-2 : 4-divinyl-6 : 7-dipropionic acid with the FeCl group replacing two H in the NH of two pyrrole rings and attached by co-ordinate links to the N atom of the two remaining rings:



By removal of FeCl by different reagents characteristic porphyrins can be obtained. With dilute acid and simple replacement of FeCl by 2H the product is **protoporphyrin**,  $C_{34}H_{34}O_4N_4$ ; hydrobromic acid gives **haematoporphyrin**,  $C_{34}H_{38}O_6N_4$ , in which two  $\cdot CH(OH) \cdot CH_3$  groups have replaced

\* *King, Rep.*, 1932, 209.

the two vinyl groups. By reduction of the vinyl groups to ethyl **mesoporphyrin**,  $C_{34}H_{38}O_4N_4$  is obtained, and by eliminating the two carboxylic groups from this by pyrolysis, **aetioporphyrin**,  $C_{32}H_{38}N_4$ , a tetramethyldiethylporphin is formed.

Theoretically 15 isomeric mesoporphyrins are possible, i.e. with the groups Me, Et, and  $\cdot CH_2 \cdot CH_2 \cdot CO_2H$  in different positions, and *Fischer* and his co-workers have synthesized 12 of these (A., 1927-31). The dimethyl esters of these mesoporphyrins are of great value in characterizing the different compounds, as they crystallize well and have definite melting-points, whereas the compounds devoid of carboxylic groups have no very definite melting-points. The synthetic mesoporphyrin which proved to be identical with that from hæmin was, by its methods of synthesis, shown to have the structure:

4Me = 1 : 3 : 5 : 8, 2Et = 2 : 4, and  $2 \cdot CH_2 \cdot CH_2 \cdot CO_2H$  = 6 and 7.

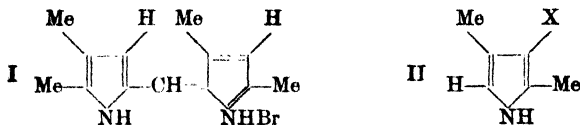
The structures of the porphyrins, (a) Aetio-, (b) Deutero-, (c) Proto-, (d) Meso-, and (e) Hæmato-, are as follows: In all five compounds methyl groups are in positions 1, 3, 5 and 8; in (a) and (d) ethyl groups are in positions 2 and 4, and in (a) also ethyl in 6 and 7. In (b) hydrogens are in positions 2 and 4, in (c) vinyl groups in 2 and 4, and in (e)  $\cdot CHMe \cdot OH$  groups in 2 and 4. In b, c, d and e the group  $\cdot CH_2 \cdot CH_2 \cdot CO_2H$  occurs in positions 6 and 7.

The method of synthesis of protoporphyrin is as follows:

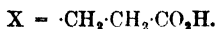
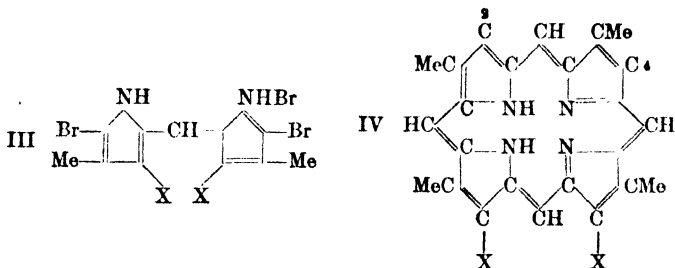
(1) 2 : 3-Dimethylpyrrole and 2 : 4-dimethylpyrrole-5-aldehyde are condensed with the aid of alcoholic hydrogen chloride to 4 : 5 : 3' : 5'-tetramethyl-2 : 2'-dipyrromethane hydrobromide, I.

(2) Cryptopyrrol-carboxylic acid, II, a degradation product of hæmin, on bromination gives 5 : 5'-dibromo-3 : 3'-di- $\beta$ -carboxethyl-4 : 4'-dimethylpyrro-2 : 2'-methene hydrobromide, III, with loss of  $CH_2$ .

(3) I and III with succinic acid at  $180^\circ$ - $190^\circ$  give deutero-porphyrin, IV, and with ferrous acetate, acetic acid, sodium







chloride and hydrochloric acid deuterohæmin is formed,\* and this with acetic anhydride in the presence of stannic chloride yields the 2:4-diacetyl derivative, and the  $\cdot\text{CO}\cdot\text{CH}_3$  groups are readily converted into secondary alcoholic groups  $\cdot\text{CH}(\text{OH})\cdot\text{CH}_3$ , giving hæmatoporphyrin, and finally heating in a high vacuum at  $105^\circ$  the  $\cdot\text{CH}(\text{OH})\cdot\text{CH}_3$  groups give  $\cdot\text{CH}:\text{CH}_2$  and a quantitative yield of protoporphyrin is obtained.

Substances isomeric with hæmin have been synthesized by similar methods (A., 1931, 491, 162).

By reducing the tervalent iron in hæmin to the bivalent state hæmochromogen is formed, and stable crystalline hæmin compounds can be obtained from proto-, aetio- and meso-porphyrin all containing bivalent iron.

Hæmoglobin is a compound of hæm with globulin, but does not give the characteristic hæmochromogen spectrum.

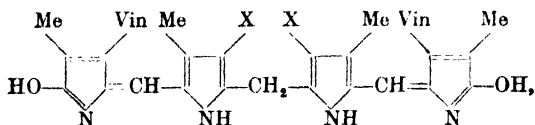
Hæmatin (hæm-oxide) forms definite additive compounds with pilocarpin, glyoxaline, &c., and the latter compound (with 8 mols. of base) is stable even at  $105^\circ$ , and in the compounds with globulin it is suggested that it is probably the glyoxaline nucleus of histidine (the characteristic amino acid of globulin) which takes part in the combination.

## 2. BILE PIGMENT

**Bilirubin**,  $\text{C}_{33}\text{H}_{36}\text{O}_6\text{N}_4$ , supposed to be formed by the degradation of hæmoglobin in the liver, is most readily obtained from ox-gall stones.

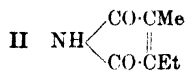
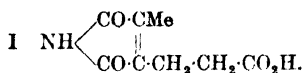
\* The iron compound is formed as it is more reactive than the iron free compound and is more readily acylated.

It has not the characteristic porphyrin ring structure, and the following formula has been suggested:

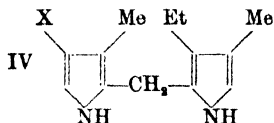
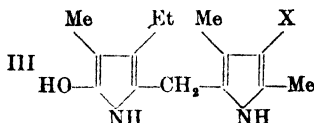


where  $\text{Vin} = \cdot\text{CH}:\text{CH}_2$  and  $\text{X} = \cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ .

Gentle reduction gives rise to **mesobilirubin**,  $\text{C}_{33}\text{H}_{40}\text{O}_6\text{N}_4$ , by the hydrogenation of the vinyl to ethyl groups, and this compound on oxidation gives hæmatic acid and methylethyl maleinimide.



On reduction with hydriodic and acetic acids mesobilirubin gives **bilirubic acid**, III, and **neobilirubic acid**, IV, and these



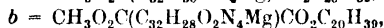
are the leuco-compounds of xanthobilirubic acid and neoxanthobilirubic acid ( $=\text{CH}-$  in place of  $-\text{CH}_2-$ , and shifting of double bonds), and both of these have been synthesized.

### 3. CHLOROPHYLL \*

The chlorophylls form the chief constituents of the green colouring matter of plant tissues; they are accompanied by the yellow colouring matters carotenes and phytoxanthins (this Chap., A.). Two related compounds, the blue-green *a* and the yellow-green *b*, are always present and usually in the ratio 3 of *a* to 1 of *b*. They are waxy solids and have not been obtained crystalline, and are best extracted from dry leaves by acetone containing 15 to 20 per cent of water. They retain small amounts of solvents and water most tenaciously,

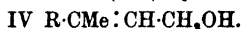
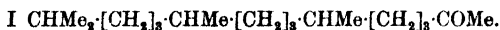
\* *Rep.*, 1935, 362; *H. Fischer*, *C. Rev.*, 1937, 41; *Steele*, *ibid.*, p. 1.

constitute about 0.8 per cent of the dry leaves, and are represented by the formulæ:



i.e. both are methyl esters of dibasic acids. When extracted with alcohol the products formed are not the chlorophylls themselves, but a methylethyl ester formed by alcoholysis in the presence of an enzyme **chlorophyllase**; if methyl alcohol is used the product is a dimethyl ester, methylchlorophyllide. When hydrolysed with alkali the chlorophylls yield methyl alcohol, phytol alcohol (phytol), and a tribasic acid **chlorophyllide**, the third carboxylic groups being formed by the fission of a ring in the chlorophyll molecule.

**Phytol** has been shown to have the structure 3:7:11:15-tetramethyl- $\Delta^2$ -hexadecene-1-ol,  $\text{CHMe}_2\cdot[\text{CH}_2]_3\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{CMe}:\text{CH}\cdot\text{CH}_2\text{OH}$ , by actual synthesis (*Fischer and Löwenberg*, A., 1929, **475**, 183) from  $\psi$ -ionone (*Chap. LVII, E.*). When catalytically reduced in the presence of palladized calcium carbonate and alcohol it gives the saturated ketone I, and this with acetylene yields II, which can be hydrogenated by hydrogen and palladized calcium carbonate to III, which passes over into IV, identical with phytol, under the action of acetic anhydride.



The same phytol has been obtained from some 200 different plants in yields of about 30 per cent of the chlorophyll present.

The magnesium in the chlorophylls and their derivatives is readily removed by dilute hydrochloric acid, e.g.  $\alpha$ -methylchlorophyllide yields  $\text{C}_{32}\text{H}_{32}\text{ON}_4(\text{CO}_2\text{Me})_2$ , known as  $\alpha$ -methylphæophorbide. Stronger acid hydrolyses one of the ester groups at the same time, yielding  $\alpha$ -phæophorbide,  $\text{C}_{32}\text{H}_{32}\text{ON}_4(\text{CO}_2\text{H})(\text{CO}_2\text{Me})$ .

The separation of  $\alpha$ - and  $b$ -chlorophylls is an extremely difficult operation, and hence a mixture of the two is converted into the  $\alpha$ - and  $b$ -phæophorbides, which can be separated by utilizing their different basicities; thus the ethereal

\* Where R represents  $\text{CHMe}_2\cdot[\text{CH}_2]_3\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{CHMe}\cdot[\text{CH}_2]_3$ .

solution of the two when shaken with 17 per cent hydrochloric acid solution gives up the *a*-compound to the acid, and the *b*-compound can be extracted by using stronger acid.

When the *a*-phæophorphide is hydrolysed by boiling for 30 sec. with methyl-alcoholic potash, *phytochlorin-e*,  $C_{31}H_{33}N_4(CO_2H)_3$ , is formed by the fission of a ring containing  $\cdot CH_2 \cdot CO \cdot$  or  $\cdot CHR \cdot CO \cdot$ .

By alkaline degradation of *phytochlorin-e* with alkali at relatively high temperatures a whole series of porphyrins can be obtained, but the final and most interesting ones are:

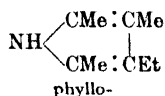
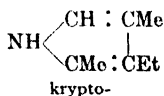
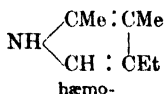
1. **Phylloporphyrin**,  $C_{31}H_{35}N_4 \cdot CO_2H$ .
2. **Pyrroporphyrin**,  $C_{30}H_{33}N_4 \cdot CO_2H$ .
3. **Rhodoporphyrin**,  $C_{30}H_{32}N_4(CO_2H)_2$ .

The first differs from the second by  $CH_2$ , i.e. replacement of  $CH_3$  by H, and this change can be effected by heating with NaOEt. The third by loss of carbon dioxide gives the second. The removal of the last  $\cdot CO_2H$  group from 1 or 2 requires distillation with soda lime or pyrolysis in high boiling solvents, and the products are termed respectively **phylloaetioporphyrin** and **pyrroaetioporphyrin**, and the former is converted into the latter by heating with sodium ethoxide.

These porphyrins are red crystalline compounds closely resembling the porphyrins from hæmin (p. 1154), e.g. meso-aetioporphyrin.

When rhodo-, phyllo- or pyrro-porphyrin or chlorin-*e* is oxidized with chromic acid, *Caro's acid* or lead peroxide, a mixture of methylethyl-maleinimide and hæmatic acid is obtained (cf. Formulæ II and I, p. 1157).

By drastic reduction with hydriodic and acetic acids phylloporphyrin yields a mixture of the 3 pyrroles:



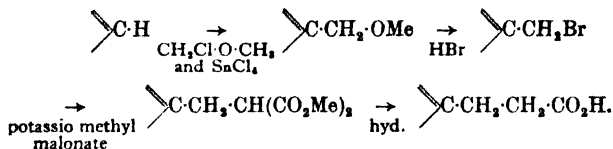
All these facts point to the presence of substituted methyl- and ethyl-pyrrol rings in the porphyrins derived from chlorophyll.

For purposes of comparison *Fischer* synthesized the 8 possible tetramethyltriethylporphyrinpropionic acids with the substituents in the position 1-8, but none was found to be identical with pyrroporphyrin; in fact it was shown that this

latter contained  $C_2H_4$  less than the synthetic products; but *Fischer* subsequently synthesized a known tetramethyltriethylporphyrinpropionic acid from pyrroporphyrin by introducing an ethyl group into the one free CH (1-8, not  $\alpha$ -8) by first acetylating and then converting the  $\cdot CO \cdot CH_3$  into  $\cdot CH_2 \cdot CH_3$  through the stages  $\cdot CH(OH) \cdot CH_3 \rightarrow \cdot CH : CH_2 \rightarrow \cdot CH_2 \cdot CH_3$ . The actual product so isolated was the 1 : 3 : 5 : 8-tetramethyl 2 : 4 : 6-triethylporphin-7-propionic acid,\* and therefore pyrroporphyrin must have a similar structure but with H in place of  $C_2H_5$  in position 2, 4 or 6.

The position was settled by the synthesis of rhodoporphyrin (A., 1930, 480, 109, 189; 482, 232) and also of phylloporphyrin. The former was shown to have the nuclear carboxylic group attached to C atom No. 6, and the latter to have an unsubstituted  $\cdot CH \cdot$  group in this position. The position of the carboxylic group is confirmed by the absorption spectra, which indicates that the  $\cdot CO_2H$  and  $\cdot CH_2 \cdot CH_2 \cdot CO_2H$  groups are in close proximity. The extra methyl group in phylloporphyrin was shown to be in the  $\gamma$ -position.

Pyrroaetioporphyrin is therefore 1 : 3 : 5 : 8-tetramethyl-2 : 4 : 7-triethylporphin, pyrroporphyrin is similar but contains  $\cdot CH_2 \cdot CH_2 \cdot COOH$  in place of Et in position 7, and rhodoporphyrin an additional  $CO_2H$  in position 6. These compounds are closely related to the porphyrins of the hæmin series, e.g. protoporphyrin is 1 : 3 : 5-trimethyl-2 : 4-divinylporphin, and on reduction gives mesoporphyrin, the corresponding diethyl compound. The passage from one series to the other has been accomplished by *Fischer*, viz. pyrroporphyrin into mesoporphyrin, by the following series of reactions at carbon atom No. 6:

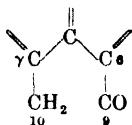


In arriving at the structure of  $\alpha$ -chlorophyll the following facts have played an important rôle.

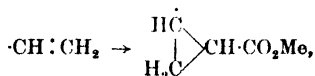
1. The magnesium free  $\alpha$ -chlorophyll, i.e.  $\alpha$ -phæophorphide (p. 1158), is readily reduced by hydriodic and acetic acids at

\* For numbering, see formula (p. 1163).

60°, giving a leuco compound which on aerial oxidation yields *phæoporphyrin-a<sub>5</sub>*,  $C_{34}H_{34}O_5N_4$ , containing a carbonyl group; on elimination of the  $\cdot CO_2H$  group this yields an extremely stable compound *phylloerythrin*,  $C_{33}H_{34}O_3N_4$ .\* This may be obtained directly from phæophorbides and other compounds by prolonged boiling with 20 per cent hydrochloric acid, and is also met with in the fæces of ruminants, e.g. sheep dung, and is evidently derived from chlorophyll by biological processes in the organism. Its structure has been established by *Fischer* both analytically and synthetically as a compound containing a five-membered carbon ring formed by the attachment of  $\cdot CO\cdot CH_2$  to carbon atoms numbered 6 and  $\gamma$ , the CO to 6 and the  $CH_2$  to  $\gamma$ . By addition of  $H_2O$  it yields phylloporphyrin ( $CH_3$  in  $\gamma$ ) and rhodoporphyrin ( $CO_2H$  in 6), corresponding with the resolution of deoxybenzoin,  $C_6H_5\cdot CH_2\cdot CO\cdot C_6H_5$ , into  $C_6H_5\cdot CH_3$  and  $C_6H_5\cdot CO_2H$ . Phæoporphyrin-*a<sub>5</sub>* contains the  $\cdot CO_2Me$  group attached to C atom No. 10.



2. The presence of one vinyl group in the place of one of the ethyl groups of pyrrporphyrin has been proved by the action of methyl diazoacetate on methyl phæophorbide (p. 1158) and chlorin-*e* trimethyl ester,

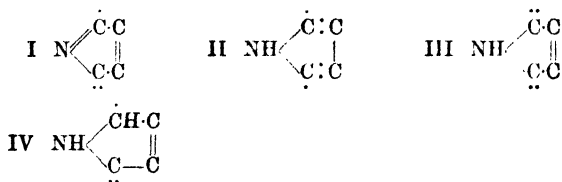


resulting in the formation of a cyclopropane derivative. All porphyrins containing saturated side chains, i.e. ethyl groups, do not react in this way. The actual position of the vinyl group, viz. No. 2, has also been established, as the oxophæoporphyrin-*a<sub>5</sub>* obtained by oxidizing the green phæophorbide in hydriodic acid has been shown to be an acetyl derivate formed by the conversion of  $\cdot CH:CH_2$  into  $\cdot CO\cdot CH_3$  at the same time that the isoporphin ring changes to the porphin

\* These formulæ correspond with the free acids, but the compounds are isolated as mono-methyl esters.

This acetyl derivative is identical with that obtained by acetylating the synthetic 1:3:5:8-tetramethyl-4-ethyl-phyloerythrin and hence must be the 2-acetyl compound.

3. An examination of physical properties such as absorption spectra, optical activity, and relative basicity of the pyrrole rings indicates that there is a difference in structure between the green derivatives of chlorophyll, e.g. phæophorphides and chlorins, and the lower degradation products the porphyrins. Thus the green derivatives give absorption bands, both visible and invisible, quite different from those of the porphyrins, and the relationship between the two is much the same as that between the derivatives of dihydrobenzene and benzene, and this suggests that the green derivatives have a dihydroporphin ring (*Connant*, J. A. C. S., 1931, 3522). *Connant* and others (*ibid.* 1930, 449; 1933, 3745; 1934, 2185) have determined the basicity of chlorophyll derivatives by potentiometric titrations, and a comparison of these values with those of pyrrole derivatives of known composition leads to the conclusion that the green derivatives contain one pyrrolinine I, two pyrrole II or *iso*-pyrrole III, and one dihydropyrrole ring IV.

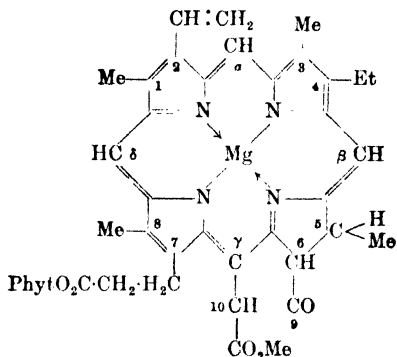


*Stoll* and *Wiedemann* (*Helv.*, 1933, 307) have shown that chlorophylls *a* and *b* and also their green derivatives are optically active, whereas the porphins derivated from them are inactive.

There is obviously a change of ring structure from *isoporphin* to porphin during degradation, and this change occurs when a phorphide or a cholin passes over to a porphyrin.

All these facts are in harmony with *Fischer's* latest formula for the chlorophyll-*a* molecule.\*

\* *Linstead* suggests that the 2H atoms are not attached to C atoms 5 and 6, but to the C joining 6 and 7 and to the adjacent N atom.

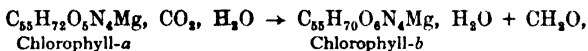


The *complete* synthesis of chlorophyll-*a* has not yet been achieved.

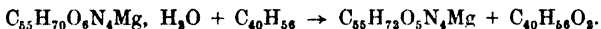
**Chlorophyll-*b*** is similar, but contains an O atom in place of 2H, and probably this is in the form of an aldehyde, CHO, group in position 3 (*Fischer, A.*, 1935, **516**, 61).

Criticisms have been raised against *Fischer's* formula.

**Phytosynthesis.\***—In the synthesis of formaldehyde and hence of glucose the ratio of oxygen evolved to carbon dioxide assimilated is always 1 : 1, the optimum temperature is 37°, and formaldehyde and not formic acid is produced. There is no very general agreement on the mechanism of the change; one view is that in sunlight chlorophyll-*a* is oxidized to the *b*-compound.



and then in the dark *b* is reduced to *a* by the aid of carotene, which is oxidized to xanthophyll:



• *Pollard*, Rep., 1936, 420. *Frank*, Chem. Rev., 1935, 433.



## LXV. SYNTHETIC DRUGS

The earlier drugs of Pharmacology were all derived from organized structures, mainly of vegetable origin, and even at the present time extracts and tinctures of plant tissues are frequently prescribed. In many cases, however, the actual active principles present in such plant tissues have been isolated, and are now generally made use of in preference to the simple plant extracts. The advantages of such pure chemical compounds are numerous: other substances with quite different physiological properties are eliminated, and correct relationships between dose and physiological effect can be established. Many of these active principles belong to the groups of compounds known as alkaloids (Chap. LVIII) and glycosides (Chap. LVI, F.). The chemical study of these compounds has, in many cases, resulted in the elucidation of their structure, and subsequently led to their synthesis, e.g. atropine (p. 1014), narcotine (p. 1008), adrenaline (p. 1179), cocaine (p. 1015).

There is still, however, a number of well-known drugs of organic origin which have not been synthesized, and which are used in large quantities in medicine; well-known examples are the alkaloids, quinine and strychnine, and the glycosides of digitalis. The synthesis of quinine substitutes has been undertaken (J. C. S., 1929, 2945, 2965; 1930, 1256; J. Ind., 1930, 757), and **plasmoquine**, 8-diethylaminoisopentylamino-6-methoxyquinoline (this Chap., I 1), is already on the market.

Not only have some of the active constituents of plants and animals been synthesized, but, in addition, numerous other synthetic products have been introduced into medicine to take the place of the older drugs. Hundreds of such compounds have been introduced: many have not received general recognition, but others have become as well known in medicine as the older drugs, e.g. phenacetin, aspirin, novocaine, &c. Many of these new synthetic drugs are manufactured from by-products obtained in the synthetic dye industry, and undoubtedly the two industries are interdependent.

The world production of pharmaceuticals (including syn-

thetics) in 1929 was estimated at £150,000,000, nearly double the value for 1913.

The syntheses of several well-known alkaloids have already been given, and in this chapter the synthetic drugs are divided into the following groups:

1. Antiseptics. 2. Hypnotics. 3. Antipyretics. 4. Diuretics and various. 5. Synthetic alkaloids and substitutes.

**Chemotherapy** is the application of chemistry to the healing of diseases, and is generally restricted to treatment by chemical substances which are much more toxic to pathogenic organisms than to the human or animal host. The term *chemotherapeutic index* = median lethal dose/minimum curative dose, where median lethal dose is the dose which will kill 50 per cent of a large number of animals. It is clear that in all cases where drugs are used internally either *per os* or by injection it is advisable to keep this ratio as high as possible (cf. *Pyman*, C and I., 1935, 580; 1937, 789). It has been proved that repeated injections with a given drug may yield strains of organisms which are highly resistant to the given drug, due probably to the fact that these strains cannot absorb the drug.

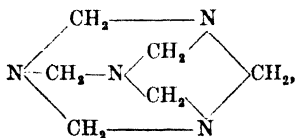
## A. Antiseptics

The function of an antiseptic is to destroy bacteria and other harmful organisms. The majority are used externally and only a few can be taken *per os*. Many are injected in order to kill deleterious organisms in the blood (cf. Trypanocides).

### 1. FORMALDEHYDE GROUP

Formaldehyde,  $\text{CH}_2\text{O}$  (p. 150) is a powerful antiseptic, and its vapour, obtained by heating paraformaldehyde, is used for disinfecting rooms. It cannot be used directly for internal use as it is highly corrosive and has toxic properties. Numerous condensation products of the aldehyde are used in medicine, and most of these owe their activity to the fact that they slowly decompose in the organism, yielding formaldehyde. The most important of such derivatives are the colourless, odourless, non-irritant products formed by condensing the aldehyde with carbohydrates, and the best known of these is the condensation product with lactose known under the name of **formamint**.

The condensation product with ammonia, viz. hexamethylene-tetramine (p. 151),



is largely used in medicine under the names **Hexamine**, **Urotropine**, &c., as a urinary antiseptic. It has strong antiseptic properties, and its aqueous solution produces no irritant effects. Numerous derivatives of hexamine have also been introduced, both as antiseptics and as uric acid eliminants, mainly as additive compounds with substances such as camphoric acid (**amphotropin**), sodium citrate, and sodium benzoate (**cystazol**). **Tannoform**, a condensation product of formaldehyde and tannic acid,  $\text{CH}_2(\text{C}_{14}\text{H}_9\text{O}_9)_2$ , is used both as an antiseptic and as an astringent.

## 2. PHENOLIC GROUP

Phenol (Chap. XXIV, A.) is one of the common organic antiseptics, and many others are hydroxylated derivatives of benzene hydrocarbons. The cresols and  $\beta$ -naphthol are more effective antiseptics than phenol and are less toxic, but suffer from the fact that they are less soluble in water. **Lysol** is a solution of cresols in soft soap.

Thymol (p. 483) is used as an antiseptic and also as a poison for intestinal parasites such as tapeworms, &c., but as a rule the carbonate,  $\text{CO}[\text{O}\cdot\text{C}_6\text{H}_3(\text{CH}_3)\text{C}_3\text{H}_7]_2$ , obtained by the action of carbonyl chloride on thymol and known as **hymatol**, is used. The polyhydric phenols are more toxic than phenol, and are made use of in treating skin diseases. The following derivative of  $\beta$ -naphthol,  $\text{OH}\cdot\text{C}_{10}\text{H}_6\cdot\underset{1}{\text{CH}_2}\cdot\underset{2}{\text{C}_6\text{H}_3}(\underset{3}{\text{OH}})\text{COOH}$ , is used in dermatology under the name of **epicarine**.

The investigations of *Bechold* and *Ehrlich* (Zeit. physiol., 1906, **47**, 173) on the general properties of substituted phenols prove that the introduction of chlorine and bromine atoms into a phenol increases its antiseptic properties, e.g. *s*-tribromophenol (p. 479) is forty-six times as active as phenol, and brominated cresols are still more active. Most of these com-

pounds, however, are too toxic for internal use. According to *R. von Walther* and *Zipper* (J. pr. Chem., 1915, **91**, 364), *p*-chloro-*m*-cresol,  $\text{OH}\cdot\text{C}_6\text{H}_3\text{Cl}\cdot\text{CH}_3$  (1 : 4 : 3), prepared by the action of sulphuryl chloride on *m*-cresol, is superior as a disinfectant to all other analogous phenol derivatives, and is used in conjunction with sodium or potassium ricinoleate to increase its solubility. Chloro-*m*-xylenol,  $\text{C}_6\text{H}_2\text{Cl}(\text{OH})\text{Me}_2$  (1 : 2 : 4 : 6) and chlorothymol are used in many antiseptics. Picric acid is an excellent germicide, and is also used for treating burns, as it kills the nerve endings.

The introduction of a 4-normal alkyl group into phenol, *m*-cresol, guaiacol or resorcinol increases their antiseptic properties, and in all cases the *n*-amyl group or the *n*-hexyl has the maximum effect (J. C. S. I., 1930, 759; J. C. S., 1930, 280). Compounds of the types 4-*n*-hexylresorcinol and 6-*n*-amyl-3-methylphenol are used in medicine. A study of the mono-*n*-alkyl ethers of resorcinol (J. A. C. S., 1931, 3397; 1932, 299) and of quinol ethers indicates a maximum effect with *n*-hexyl or *n*-nonyl in the former and *n*-amyl or *n*-octyl in the latter, according to the organism examined. In these and in many other cases the higher—butyl to nonyl—radicals are more effective than the simple methyl and ethyl groups, e.g. the ethers of harmol (Bio. J., 1933, 727; 1934, 264). The branching of a chain tends to lessen the therapeutic activity of a group. It is interesting to note that the only ethers occurring naturally are methyl ethers.

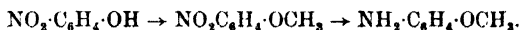
The introduction of a carboxylic group into the phenol molecule lowers both its toxic and antiseptic properties, and *o*-hydroxybenzoic acid, or salicylic acid, and its salts are common antiseptics (for synthesis, cf. p. 525), as is also the phenyl ester of salicylic acid known as **salol**,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{C}_6\text{H}_5$  (p. 525), which is used as a bladder and intestine antiseptic. The chief use, however, for salicylic acid and its salts in medicine is for cases of acute rheumatism, when its action is most marked. As the acid and its salts produce gastric troubles, they have been largely replaced by acetyl-salicylic acid, **aspirin**,  $\text{CH}_3\cdot\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{COOH}$ , and its salts. The sodium salt is **tylnatrin** and the calcium **kalmopyrin**. The natural glucoside, **salicin** (p. 947), is sometimes administered, as in the organism it is hydrolysed to glucose and salicyl alcohol, which is slowly oxidized to salicylic acid.

Sodium cinnamate (**hetol**) has been recommended in cases of

tuberculosis, in aqueous or better in glycerol solutions, and *m*-cresyl cinnamate,  $C_6H_5 \cdot CH : CH \cdot COOC_6H_4 \cdot CH_3$ , known as **hetocresol**, is used as a dusting powder for tuberculous wounds.

In the organism salol is hydrolysed very slowly to phenol and salicylic acid, and both of these exert their antiseptic properties. The method of synthesis of salol has been used for the preparation of numerous other esters derived from salicylic acid and also from other acids. Some of these esters can also be prepared by heating salol with another phenol, e.g. quinol, eugenol, carvacrol. **Monosalicylin**,  $OH \cdot CH_2 \cdot CH(OH) \cdot CH_2 \cdot O \cdot CO \cdot C_6H_4 \cdot OH$ , is known as *glycosal*. **Methyl acetylsalicylate**,  $CH_3 \cdot CO \cdot O \cdot C_6H_4 \cdot COOCH_3$ , is *methylrodin*, and **methyl benzoylsalicylate** is *benzosalin*.  **$\beta$ -Naphthyl salicylate**, which is next in importance to salol, is known as *betol* or *naphtholsalol*, **menthyl salicylate** is *salit*, and **phenyl salicylate** is *disalol*.

Guaiacol (p. 484) and its derivatives are also used for medicinal purposes. A common synthesis is from *o*-nitrophenol (p. 480), which is transformed into *o*-anisidine in the following stages:



The anisidine is then diazotized, and the solution poured into a mixture of sulphuric acid and sodium sulphate at  $135^\circ$ – $160^\circ$ , when the guaiacol distils over. **Guaiacyl carbonate** or *duotal*,  $(OCH_3 \cdot C_6H_4 \cdot O)_2CO$ , made from the sodium derivative of guaiacol and carbonyl chloride, is less toxic than guaiacol. **Guaiacyl phosphite**, *phospatol*,  $P(O \cdot C_6H_4 \cdot OCH_3)_3$ , from phosphorus trichloride and an alkaline solution of guaiacol, the benzoate, cinnamate, acetate, and cacodylate have all been prepared. The monoglyceryl ether, **guaiamar**,  $OH \cdot CH_2 \cdot CH(OH) \cdot CH_2 \cdot O \cdot C_6H_4 \cdot OCH_3$ , from monochlorhydrin (p. 230) and alkaline guaiacol, is soluble in water, and is hydrolysed to its components in the organism. **Potassium guaiacol-3-sulphonate**,  $OH \cdot C_6H_3(OCH_3)SO_3K$ , known as *thiocol*, is less irritant than guaiacol.

**Dermatol**, a derivative of gallic acid, viz. basic bismuth galate,  $C_6H_2(OH)_3 \cdot COOBi(OH)_2$ , is an iodoform substitute.

Salts of mandelic acid (p. 529) are largely used as urinary antiseptics.

## 3. IODINE COMPOUNDS

Various iodine derivatives are used as antiseptics, the best known of which is the external antiseptic **iodoform**,  $\text{CHI}_3$  (p. 68). A compound of iodoform with hexamethylenetetramine, known as **iodoformin**, is odourless, as is also the compound with hexamethylene-tetramine-ethyl-iodide known as **iodoformal**. Both compounds are decomposed by water into their components. **Iodothion**, 1-iodo-2:3-di-hydroxypropane,  $\text{CH}_2\text{I}\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{OH}$ , is formed by the action of potassium iodide on glycerol and chlorhydrin. **Iodol** or **tetraiodopyrrole** is odourless and non-irritant, and resembles iodoform in the fact that its action is probably due to the liberation of iodine. It is prepared by the action of iodine on an alkaline solution of pyrrole (p. 662).

Compounds of the type of *s*-triiodo-*m*-cresol prepared by the action of iodine on  $\text{C}_6\text{H}_3(\text{CH}_3)(\text{OH})\text{CO}_2\text{H}$  (1:3:4), or on *m*-cresol, resemble phenol in antiseptic properties, e.g. *aristol*, diiododithymyl or 2:2-dimethyl-3:3'-diiodo-4:4'-diisopropyl-6:6'-dihydroxydiphenyl,  $\text{C}_3\text{H}_7\cdot\text{C}_6\text{H}_2\text{Me}(\text{I})\cdot\text{C}_6\text{H}_2\text{Me}(\text{C}_3\text{H}_7)\cdot\text{I}$ . Another type of iodine derivative is *p*-**iodoxy-toluene**, *isoform*,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{IO}_2$ , valuable as a dry antiseptic.

## 4. SULPHANILAMIDE GROUP

**Sulphanilamide**, *p*-aminobenzenesulphonamide,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\text{NH}_2$ , has proved invaluable as an internal anaesthetic, and is used for various types of streptococcal infection, including puerperal fever, general septicæmia, erysipelas, peritonitis, arthritis, tonsillitis, meningitis, also for various types of pneumococcal infections, e.g. cerebrospinal meningitis, pneumonia, and for staphylococci, e.g. carbuncles, abscesses, &c., and infections due to *Bacillus coli*.

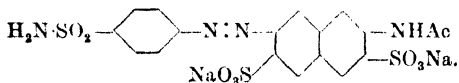
Numerous derivatives of sulphanilamide and allied compounds have been examined to test their bactericidal activity. It is essential that there should be a sulphur atom para to the amino group. Sulphanilic acid itself is only slightly active and benzenesulphonamide is entirely inactive. The introduction of other groups into the ring tends to minimize the activity, but the introduction of aldehyde residues (*Schiff's* bases) of an aminated acyl group into the amino group increases the activity. One of the most active compounds is 4:4'-diaminodiphenylsulphone,  $(\text{NH}_2\cdot\text{C}_6\text{H}_4)_2\text{SO}_2$ , but it is also highly

toxic; the corresponding diacetyl derivative is also highly active and much less toxic, and the 4-amino-4'-hydroxy compound is active and not too toxic. 2-*p*-Aminobenzene sulphonamidepyridine (*p*-aminobenzpyridylsulphonamide) (*p*)-NH<sub>2</sub>·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>·NH<sub>2</sub>Pyr, is very effective in cases of pneumonia.

N-Dodecanoylsulphanilamide is stated to be more effective than the simple compound in cases of tuberculosis and streptococcal infections; it has a low toxicity and a high degree of solubility in fat.

Other compounds of this type are:

The **Prontosils** are sulphonamides containing an azo group. Prontosil itself is 2:4-diamino-azobenzene-4'-sulphonamide, (NH<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>:N:N·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>·NH<sub>2</sub>, and is a most effective remedy for practically all the infections referred to in the case of sulphanilamide, and its action is attributed to the formation of this latter compound in the body. Soluble prontosil or prontosil S contains a naphthalene ring:



These compounds have come into general use since 1935, as they are readily administered *per os* and are not too toxic.

*Proseptasine*, *p*-C<sub>6</sub>H<sub>5</sub>·CH<sub>2</sub>·NH·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>·NH<sub>2</sub>; *Soluseptacine*, disodium *p*-( $\gamma$ -phenylpropylamino)-benzene-sulphonamide- $\alpha\gamma$ -disulphonate, SO<sub>3</sub>Na·CHPh·CH<sub>2</sub>·CH(SO<sub>3</sub>Na)·NH·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>·NH<sub>2</sub>; *uleron*, *p*-aminobenzene-sulphonyl-*p*'-aminobenzene-sulphone-di-methylamide, NH<sub>2</sub>·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>·NH·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>NMe<sub>2</sub>; and *Disseptal* (*p*-aminobenzene-sulphonyl-*p*'-aminobenzene-sulphone-methylamine) with the ·SO<sub>2</sub>·NHMe in place of ·SO<sub>2</sub>·NMe<sub>2</sub>, are also of value.

## 5. CHLORAMINE GROUP

The group of organic compounds containing Cl attached to N, viz. the **chloramines**, are valuable antiseptics. Their physiological action is similar to that of hypochlorite, but they are less irritant and much more stable, and it is easy to obtain aqueous solutions of definite strength. They are largely used for treatment of infected wounds, and are prepared by the action of hypochlorite solutions on compounds containing

the NH or NH<sub>2</sub> groups (cf. *Chattaway*, J. C. S., 1905, 145). The commonest of these compounds is sodium *p*-toluene-sulphonechloramide, CH<sub>3</sub>·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>·NClNa, 3H<sub>2</sub>O, known generally as **chloramine T** or **tolamine**. It is made from *p*-toluene-sulphonylchloride, CH<sub>3</sub>·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>Cl, a by-product in the manufacture of saccharine (p. 519). This is converted by the action of ammonia into the corresponding amide, which yields chloramine T when warmed with sodium hypochlorite solution.

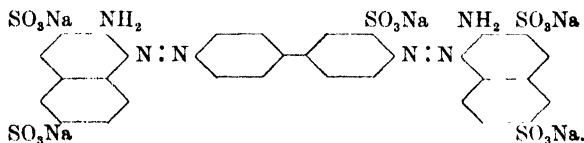
The corresponding dichloro-derivative, *dichloramine T*, made from *p*-toluenesulphonamide by the action of bleaching-powder, and the carboxylic acid, *p*-sulphone-dichloraminobenzoic acid, *halazone*, CO<sub>2</sub>H·C<sub>6</sub>H<sub>4</sub>·SO<sub>2</sub>·NCl<sub>2</sub>, prepared by oxidizing *p*-toluenesulphonamide with dichromate and sulphuric acid and treating an alkaline solution of the product with chlorine, are both good disinfectants. The latter is used for sterilizing drinking-water.

## 6. GROUP OF ANILINE DYES

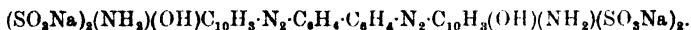
Many aniline dyes have antiseptic properties, and several of these have found use in medicine, more particularly for destroying the protozoa characteristic of certain diseases. A few of the more important dyes used are:

### (a) Azo Compounds.

**Trypan red**, obtained by diazotizing both amino-groups in benzidineorthosulphonic acid, NH<sub>2</sub>·C<sub>6</sub>H<sub>4</sub>·C<sub>6</sub>H<sub>3</sub>(SO<sub>3</sub>H)·NH<sub>2</sub>, and coupling the tetrazonum salt with 2-naphthylamine-3 : 6-disulphonic acid. Its structural formula is:



**Trypan blue** is obtained by diazotizing *o*-tolidine (p. 545) and coupling the tetrazo-compound with 8-amino-1-naphthol-3 : 6-disulphonic acid, and has the formula:



Characteristic of the dyes of the benzidine series possessing trypanocidal properties is the presence of sulphonic acid groups in the 3 : 6 positions.

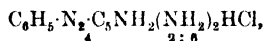


**Brilliant green**, the sulphate of the ethyl base corresponding with malachite green (p. 555), prepared from benzaldehyde, diethylaniline, sulphuric acid, and an oxidizing agent such as lead peroxide, has the structure  $\text{NEt}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C}(\text{C}_6\text{H}_5) : \text{C}_6\text{H}_4 : \text{NEt}_2 \cdot \text{HSO}_4$ , and is largely used as a general antiseptic.

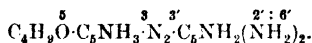
Methylene blue (p. 1053) is used internally for various diseases, including rheumatism, nephritis, &c., and other dyes are methyl violet and crystal violet.

### (b) Pyridine Derivatives.

Derivatives of 2-amino- and 2:6-diaminopyridine are of great value as drugs, and the azo-compounds (p. 686) are antiseptics, especially **pyridium**, phenylazo-2:6-diaminopyridine hydrochloride,



and **neotropin**,

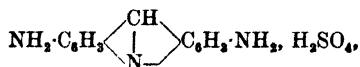


obtained by coupling diazotized 2-butoxy-5-aminopyridine with 2:6-diaminopyridine.

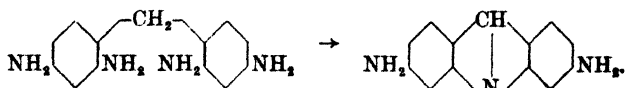
For arseno-compounds, cf. Chap. LXVI.

### (c) Acridine Derivatives.

**Proflavine**, or 3:6-diamino-acridine-sulphate,

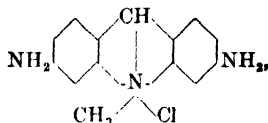


is prepared synthetically from *p-p*-diamino-diphenylmethane: this is nitrated, and then reduced with tin and hydrochloric acid, when 2:4:2':4'-tetra-amino-diphenylmethane is obtained. The solution containing the reduction product in the form of its stannichloride is heated in an autoclave at 140°, when ring formation occurs, ammonia is eliminated, and 3:6-diamino-acridine is obtained:



It is useful in cases of meningitis and gonorrhoea.

**Acridavine, 3 : 6-diaminomethylacridinium chloride,**



is obtained by acetylating proflavine, methylating the tertiary nitrogen atom by means of methyl sulphate, and then eliminating the acetyl groups and heating with hydrochloric acid. **Rivanol** has OEt in 7 and NH<sub>2</sub> in 3 and 9. The acridine dyes are used for the treatment of wounds; they are highly antiseptic and devoid of irritant or toxic action, and do not inhibit the process of healing.

## B. Hypnotics and Anæsthetics

The oldest of these is morphine, but it has now been largely replaced by synthetic materials which are free from the unpleasant and dangerous properties of morphia. General anæsthetics are closely related to hypnotics from a physiological standpoint, but are usually volatile compounds, which are administered by inhalation, as their effects are then so much more rapid and the duration much more readily controlled.

The hypnotics and general anæsthetics belong to various groups of carbon compounds. General anæsthetics comprise the group of halogen derivatives of aliphatic hydrocarbons and the group containing alkyl, particularly ethyl, groups. The non-volatile narcotics include compounds of these types, and also many compounds containing the carbonyl group, and others contain a heterocyclic nitrogen ring.

Various attempts have been made to establish relationships between hypnotic action and physical properties. In many cases it is found that in a given series of hypnotics the physiological activity increases with the distribution coefficients of the substances for fat and water, or, in other words, with the rapidity of diffusion of the substance into protoplasm (*Overton, H. Meyer*). There are various substances, however, which have a high distribution coefficient, but are without hypnotic action. According to *Traube*, the osmotic permeability, or, in

other words, the surface tension of the substance, determines the narcotic action. In reality both surface tension and the distribution coefficient are important physical factors affecting hypnotic action. *Baglioni* suggests that the narcotic action is due to deprivation of oxygen, and it has been shown that chloroform, ether, and chloral hydrate diminish the oxidizing capacity of tissues.

### 1. HALOGEN ANÆSTHETICS AND HYPNOTICS

The best-known halogen anæsthetic is chloroform (p. 68). Pure chloroform is unstable, and is decomposed by air and moisture, yielding phosgene, which is highly injurious. This decomposition is prevented by the addition of about 2 per cent of ethyl alcohol.

A German process for the manufacture of chloroform consists in saturating alcohol (95 per cent) with chlorine, and then allowing the chlorinated product to flow over calcium hydroxide mixed with a little bleaching-powder. The other halogen derivatives of methane also possess hypnotic action, which tends to increase with the amount of chlorine present; thus carbon tetrachloride is more effective than chloroform, but is not generally used, as it is more toxic. Ethyl chloride (p. 64) is used both as a general and a local anæsthetic, but its use for the latter is simply due to the low temperature produced by its rapid evaporation. Practically all halides with boiling-point between  $25^{\circ}$ – $60^{\circ}$  can be used in place of ethyl chloride. Chloral hydrate, which is non-volatile, is a common hypnotic; it cannot be injected subcutaneously, as it has a deleterious after-effect on the heart. Its activity is not due to the formation of chloroform, as trichloroethyl alcohol and not chloroform is formed in the system. Many compounds and derivatives of chloral are used, but all these depend on the primary liberation of chloral, and have few or no advantages over chloral hydrate. Chloral formamide,  $\text{CCl}_3\cdot\text{CH}(\text{OH})\cdot\text{NH}\cdot\text{CHO}$  (*chloralamide*), is a mild hypnotic and sedative. **Dormiol**,  $\text{CCl}_3\cdot\text{CH}(\text{OH})\cdot\text{O}\cdot\text{CMe}_2\cdot\text{CH}_2\cdot\text{CH}_3$ , is a condensation product of chloral and tertiary amyl alcohol. Chloral urethane,  $\text{CCl}_3\cdot\text{CH}(\text{OH})\cdot\text{NH}\cdot\text{CO}_2\text{C}_2\text{H}_5$ , yields a soluble ethyl derivative known as **somnal**.

Tertiary trichlorobutyl alcohol,  $\text{CCl}_3\cdot\text{C}(\text{CH}_3)_2\text{OH}$ , **chlore-tone**, obtained by condensing acetone and chloroform in the

presence of solid potassium hydroxide, is a crystalline solid, m.-pt.  $96^{\circ}$ , and has no irritant action on the stomach but acts as a sedative. It is largely used in U.S.A. in cases of sea-sickness and vomiting. Bromal hydrate in large doses has an anæsthetic action. Various bromine derivatives act as mild hypnotics. Some of these are: **bromopin**, a compound of bromine and sesamé oil which can be used as a substitute for potassium bromide; sodium  $\alpha$ -bromoisovalerate, **valerobromine**,  $\text{CH}(\text{CH}_3)_2 \cdot \text{CHBr} \cdot \text{CO}_2\text{Na}$ ; bornyl  $\alpha$ -bromoisovalerate,  $\text{CH}(\text{CH}_3)_2 \cdot \text{CHBr} \cdot \text{CO}_2\text{C}_{10}\text{H}_7$ , **bromovalol** or **eubornyl**, and  $\alpha$ -bromoisovalerylurea,  $\text{CH}(\text{CH}_3)_2 \cdot \text{CHBr} \cdot \text{CO} \cdot \text{NH} \cdot \text{CO} \cdot \text{NH}_2$ , **bromurul** or **dormigene**, and also bromo-derivatives of protein, e.g. **bromoglydine** and **bromalbin**. Analogous iodine compounds are also used, e.g. **iodipin**, analogous to bromopin, **iodival**, or iodoisovalerylurea, and iodo-derivatives of proteins; most of these compounds are used as substitutes for alkali iodides which often produce unpleasant symptoms.

## 2. ETHYL ANÆSTHETICS

A second important group of anæsthetics comprises the compounds containing alkyl groups attached to OH or O. Methyl groups appear to be inactive, but compounds containing ethyl, and especially tertiary alkyl groups, e.g.  $\cdot\text{CMe}_3$ ,  $\cdot\text{CMe}_2\text{Et}$ , and  $\text{CEt}_3$ , have strong hypnotic action. Ethyl alcohol is useless, as very large doses are required to produce sleep, probably owing to the readiness with which it is oxidized in the tissues, and higher alcohols are not employed, as they are not readily volatile. Ethyl ether is a very common anæsthetic. Other ethers, e.g.  $\text{EtOMe}$  and  $\text{MeOPr}$ , have similar effects but are more expensive. Ethylene is also used and also vinyl ether, **vinethane**,  $\text{O}(\text{CH}:\text{CH}_2)_2$ , as substitutes for nitrous oxide; also carefully purified acetylene in conjunction with oxygen.

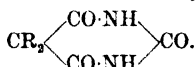
Derivatives of urea containing a tertiary alkyl group are also efficient hypnotics, tertiary-amyl-urea,  $\text{NH}_2 \cdot \text{CO} \cdot \text{NH} \cdot \text{CMe}_2\text{Et}$ , being one of the best. Numerous ureides are also used.

**Amides and Ureides: Barbituric Acids.**—Certain acyclic amides, e.g. bromacetamide,  $\text{CH}_2\text{Br} \cdot \text{CO} \cdot \text{NH}_2$ , have slight hypnotic properties which are greatly increased by the intro-

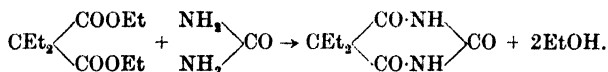
duction of ethyl groups. The compound  $\text{C}_2\text{H}_5\text{Br}\cdot\text{CO}\cdot\text{NH}_2$  was employed for years under the name of **neuronal**, but has become replaced by **novonal**, diethylallylacetamide,  $\text{CH}_2\text{:CH}\cdot\text{CH}_2\cdot\text{C}_2\text{H}_5\cdot\text{CO}\cdot\text{NH}_2$ , obtained from ethyl cyanoacetate by the following stages: alkylated to diethyl compound, hydrolysed and  $\text{CO}_2$  eliminated, yield diethylacetoneitrile, alkylated with K and allylbromide to the allyldiethyl nitrile, and partially hydrolysed to the amide.

Ureides, i.e. acylated ureas (Chap. XIII, C.), are more active than amides.

Of the monoureides (p. 322) those containing a bromine atom are of value, e.g.  $\alpha$ -bromoisovalerylcarbamide,  $\text{CHMe}_2\cdot\text{CHBr}\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}_2\cdot\text{NH}_2$ , is **uvaleral** or **dormigene**, and **uradal** or **adalin** is  $\text{Br}\cdot\text{C}_2\text{H}_5\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$ . Numerous diureides are used, particularly the substituted (dialkylated) barbituric acids,



Diethylmalonylurea or diethylbarbituric acid is the well-known **veronal** or **barbitone**; the activity of the corresponding dipropyl compound is so intense that it is too dangerous for general use. Butylethyl is **soneryl** and diallyl is **dial**. **Luminal** is the phenyl ethyl compound. The allyl isopropyl compound is used with antipyrine under the name **allional**. **Noctal** is isopropyl-bromopropenyl-barbituric acid  $\text{CPr}^{\text{H}}\cdot\text{CH}\cdot\text{CBr}\cdot\text{CH}_3$  in place of  $\text{C}_2\text{H}_5$ ; veronal is 5 times as active as the latter. **Dormalgin** contains the secondary butyl in place of the secondary propyl group of noctal, and is used in childbirth and frequently used in conjunction with pyrimidone. These dialkylated barbituric acids can be prepared by condensing dialkylmalonic esters with urea in the presence of sodium ethoxide:



Many of the urethanes (p. 317) exhibit hypnotic properties; the best known of these is **hedonal**, methylpropylcarbinyl urethane,  $\text{NH}_2\cdot\text{CO}\cdot\text{OCH}(\text{CH}_3)\text{C}_3\text{H}_7$ , prepared by the action of urea nitrate on methylpropylcarbinol.

Most ketones can act as hypnotics. Those containing ethyl groups are more active than those containing methyl; the

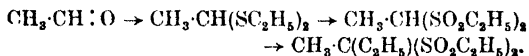
true aromatic ketones have only a mild action, but mixed ketones, e.g. acetophenone, **hypnone**,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3$ , and phenyl ethyl ketone,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{C}_2\text{H}_5$ , are much more active.

### 3. SULPHONES

A group of great practical importance are the sulphone derivatives, the most important representatives of which are **sulphonal** dimethylmethane-diethylsulphone,  $\text{C}(\text{CH}_3)_2(\text{SO}_2\text{C}_2\text{H}_5)_2$ , and **trional**,  $\text{CH}_3\cdot\text{C}(\text{C}_2\text{H}_5)(\text{SO}_2\text{C}_2\text{H}_5)_2$ . A comparison of the

whole series of compounds  $\begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{R}^2 \end{array} \begin{array}{c} \text{SO}_2\text{R}^3 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{SO}_2\text{R}^4 \end{array}$  has proved that to

produce a compound with hypnotic properties it is necessary that  $\text{R}^3$  and  $\text{R}^4$  should be ethyl groups, and  $\text{R}^1$  and  $\text{R}^2$  methyl or ethyl. The most powerful is tetronal, where all 4 radicals are ethyl, but it is poisonous. Sulphonal is manufactured by condensing acetone and ethyl mercaptan in the presence of hydrogen and calcium chlorides, and oxidizing the resulting mercaptol with excess of permanganate (p. 161). Trional can be prepared in a similar manner by replacing acetone by methyl ethyl ketone. An alternative method is to condense acetaldehyde with ethyl mercaptan, oxidize the mercaptol, and then ethylate with ethyl iodide and alkali:

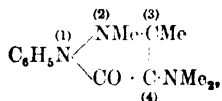


For local anæsthetics, cf. this Chap., I4.

## C. Antipyretics

Quinine is able to reduce the body temperature in cases of fever, i.e. it is an antipyretic, but at the same time it has a specific effect against malaria. The first synthetic experiments were made with the object of obtaining substances comparable with quinine, which was known to be a quinoline derivative, although its structure was not then established. Various alkylated tetrahydroquinolines were prepared and shown to possess antipyretic action; **kairine**, 1-ethyl-5-hydroxytetrahydroquinoline, is one of the most effective, but all these compounds are useless as they are toxic to red

blood corpuscles. *Knorr* was the first to produce a valuable synthetic antipyretic in 1887 in the substance known as **antipyrine**, **phenazone** (p. 676). This compound has greater antipyretic activity than quinine, but has no specific action against malaria. Like many of the synthetic antipyretics, it has a powerful analgesic action, i.e. it can act on the nervous system and soothe pain, especially neuralgic pain. Numerous derivatives have been put on the market, but most of these are not superior to the original antipyrine. A valuable derivative is **pyramidon**, 4-dimethylamino-antipyrine:

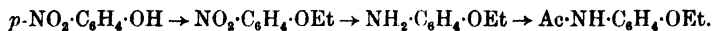


which is prepared by the following process from antipyrine: nitrous acid yields the 4-nitroso derivative, and this is readily reduced to the corresponding amine, which when methylated yields pyramidone. A better method is to condense 4-amino-antipyrine with nitrosodimethylamine, yielding a compound with the  $\cdot\text{N}:\text{N}\cdot\text{NMe}_2$  group in position 4, which with copper powder yields  $\text{N}_2$  and pyramidon.

The cheapest of all antipyretics is acetaniline (**antifebrine**) (p. 445). It has valuable antipyretic and analgesic properties, but suffers from the defect that aniline is gradually liberated in the system, and symptoms of aniline poisoning may become apparent. Various other anilides have been suggested for use but have met with little favour.

Phenylurethane,  $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{CO}_2\text{C}_2\text{H}_5$  (**euphorin**), from ethyl chloroformate and aniline, has marked analgesic properties.

**Phenacetin**, *p*-ethoxyacetanilide,  $\text{OC}_2\text{H}_5\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$  (p. 481), is the best-known representative of the *p*-aminophenol derivatives, and the corresponding methoxy derivative is even more active, but is also more toxic. It can be prepared in a variety of ways, e.g.



The propyl and butyl ethers are much less active. The idea that derivatives of *p*-aminophenol might be useful as drugs was suggested by the observation that this is the main product formed when aniline and its simple derivatives are introduced into the organism. Numerous derivatives of phenacetin have

been tried but none has any advantage; in all cases the therapeutic effect appears to be due to the liberation of *p*-aminophenol or of its ethyl ether in the tissues. The ethyl derivative,  $\text{OEt}\cdot\text{C}_6\text{H}_4\cdot\text{NEt}\cdot\text{CO}\cdot\text{CH}_3$ , is even more efficient than phenacetin, but its higher cost militates against its use. Numerous compounds in which the acetyl group of phenacetin is replaced by other acyl groups, e.g. lactyl, diacetyl, salicyl, mandetyl, have been examined but are not so effective as the acetyl compound. Its salt with salicylic acid is used under the name **salipyrin**. Various condensation products of phenetidine,  $\text{OC}_2\text{H}_5\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$ , with aldehydes have been prepared, e.g. with salicylaldehyde, vanillin, and vanillin ethyl carbonate. Amino-phenacetin, **phenocoll**,  $\text{OEt}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{NH}_2$ , prepared from ammonia and bromoacetylphenetidine, is similar in action to phenacetin; it has a greater analgesic action, and is a good substitute for salicylic acid in cases of rheumatic fever.

**Salophen**,  $\text{NHAc}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\cdot\text{C}_6\text{H}_4\cdot\text{OH}$ , the salicylic ester of *p*-acetaminophenol, is also used.

The commonest antipyretic is acetylsalicylic acid,  $\text{CH}_3\cdot\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H}$ , **aspirin**, and is made by the action of acetyl chloride and zinc chloride, or of sodium acetate and acetic anhydride, on the acid. Salicylosalicylic acid, **diplosal**,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{H}$ , and succinylsalicylic acid, **di-aspirin**, are also used. **Salophene** (p. 526),  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\cdot\text{C}_6\text{H}_4\cdot\text{NHAc}$  (*p*), has no taste and no odour, and is used as a substitute for aspirin. **Spirosal**,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , is made from sodium salicylate,  $\text{C}_2\text{H}_4\text{Br}_2$ , and water. Sodium salicylate is a common drug for rheumatism of the joints.

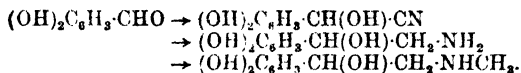
## D. Sympathomimetica

Drugs with sympathomimetic action are those which stimulate the sympathetic nervous system, produce rise in blood pressure by contracting blood vessels and reduce the peristaltic movements of the intestine. They are frequently used in conjunction with local anæsthetics to prevent excessive hæmorrhage. The simplest is 2-phenylethylamine,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$ , and more active are aryl ethanolamines,  $\text{Ar}\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{NH}_2$ .

The most important of these is *l*-adrenaline, 3 : 4-(OH) $_2$ C<sub>6</sub>H<sub>3</sub>.

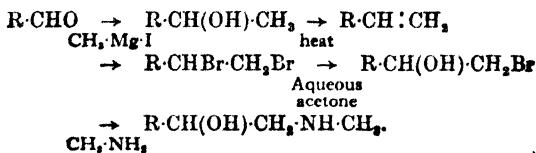


$\text{CH(OH)}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CH}_3$ , a crystalline compound obtained from the suprarenal glands (*Takamine*, Am. J. Pharm., 1901, **73**, 523; for constitution, compare *Jowett*, J. C. S., 1904, 192). The constitution is confirmed by the fact that the ketonic oxidation product adrenalone is identical with the synthetic compound derived from methylamine and chloroacetylcatechol, and must be represented as  $(\text{OH})_2\text{C}_6\text{H}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CH}_3$  (*Friedmann*). Adrenaline is formed when the sulphate of the amino-ketone is reduced with aluminium amalgam or electrolytically. An interesting synthesis (Jap. Pats., 1918) is from protocatechuic aldehyde; this is converted into the diacetyl derivative, which condenses with nitromethane in feebly alkaline solution, giving  $\beta$ -hydroxy:  $\beta$ -3: 4-diacetoxyphenylnitroethane  $(\text{OAc})_2\text{C}_6\text{H}_3\cdot\text{CH(OH)}\cdot\text{CH}_2\cdot\text{NO}_2$ ; when this is mixed with formaldehyde and reduced with zinc and acetic acid, the diacetyl derivative of adrenaline  $(\text{OAc})_2\text{C}_6\text{H}_3\cdot\text{CH(OH)}\cdot\text{CH}_2\cdot\text{NHMe}$  is formed, and this on hydrolysis gives adrenaline. *r*-Adrenaline can also be prepared by condensing protocatechuic aldehyde with hydrogen cyanide, reducing the resulting nitrile to the primary amine, which is then methylated:



The racemic compound can be resolved by means of *d*-tartaric acid and also by means of *Penicillium glaucum*. This method is not used commercially. It is interesting to note that the *l*-compound is about twelve times as active physiologically as the corresponding *d*-compound. The ketone adrenalone (cf. above) is not so active as adrenaline, and two alkyl groups attached to the N atom diminish the activity.

The methylene and dimethyl ethers of adrenaline have also been synthesized, e.g. the dimethyl from veratraldehyde and the methylene ether from piperonal (p. 497), as denoted by the following scheme, where R represents either the  $(\text{OMe})_2\text{C}_6\text{H}_3$  or  $\text{CH}_2\text{O}_2\text{C}_6\text{H}_3$  groups:

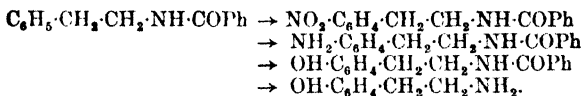


Adrenaline is largely used in conjunction with the local anæsthetics cocaine and eucaine, as it tends to check bleeding; it is also used to neutralize the toxic effects of cocaine, and is used as a specific for hay fever.

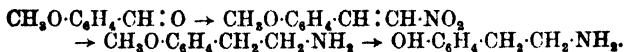
The parent substance of the group of adrenaline derivatives, viz. parahydroxyphenylethylamine, **tyramine**,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$ , can be obtained by elimination of carbon dioxide from tyrosine (pp. 526 and 1210),  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}(\text{CO}_2\text{H})\cdot\text{NH}_2$ ; it is present in putrid meat, and is undoubtedly derived from the tyrosine present in the meat, just as phenylethylamine and isoamylamine, which are also present in putrid meat, are derived from the corresponding carboxylic derivatives, phenylalanine (pp. 521 and 1210) and leucine (p. 1210). Parahydroxyphenylethylamine is also present in the aqueous extract of the drug ergot, and its synthesis has led to its therapeutic use. The following synthetical methods have been adopted:

1. *p*-Hydroxybenzyl cyanide on reduction with sodium and alcohol yields the amine (*Barger*, J. C. S., 1909, 1123).

2. Phenylethylamine from benzylcyanide is benzoylated and then nitrated, the nitro compound is reduced to the corresponding amine, and this, by means of nitrous acid, transformed into the hydroxy derivative, and finally the benzoyl group is removed by hydrolysis (*Barger and Walpole*, *ibid.* 1720).

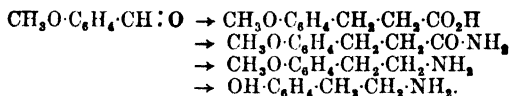


3. Anisaldehyde and nitromethane react in the presence of dilute alkali, yielding  $\beta$ -nitro-*p*-methoxystyrene; this is reduced to the corresponding saturated amine, and the methyl ether converted into the free phenol by means of hydriodic acid (*Rosenmund*, B., 1909, 4778):



4. Starting with anisaldehyde, *p*-methoxycinnamic acid is prepared by condensing with ethyl acetate in the presence of finely divided sodium. This acid is reduced to the corresponding saturated acid, which is converted into its chloride

and then into the amide, which, by the *Hofmann* reaction, yields the amine. The last stage consists in converting the methoxy into the hydroxy group by means of concentrated hydrobromic acid:



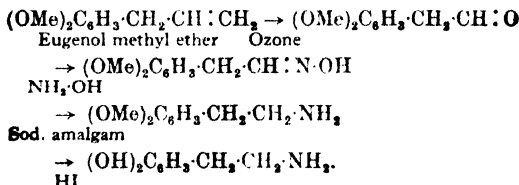
***l*-Ephedrine**,  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CHMe}\cdot\text{NHMe}$ , 1-phenyl-2-methyl-amino-propan-1-ol, occurs in species of *ephedra*, and the *d*-*l*-base can be synthesized by condensing benzaldehyde with nitroethane to 1-phenyl-2-nitro-propan-1-ol,  $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{NO}_2)\cdot\text{CH}_3$ , reducing to the corresponding 2-hydroxyamino-compound  $\cdot\text{NH}\cdot\text{OH}$ , condensing with formaldehyde to the

methylenenitrone  $\text{—N} \begin{array}{l} \diagup \text{O} \\ | \\ \diagdown \text{CH}_2 \end{array}$ , and final reduction to the

*d*-*l*-alkaloid. Another method is from benzene and  $\alpha$ -bromopropionyl bromide to  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CHMeBr}$ , which with  $\text{CH}_3\cdot\text{NH}\cdot\text{SO}_2\text{C}_2\text{H}_5$  gives  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CHMe}\cdot\text{NMe}\cdot\text{SO}_2\text{C}_2\text{H}_5$ , and this on hydrolysis and reduction yields ephedrine. It can be administered *per os*, is absorbed less quickly, and its action is less intense than that of adrenaline.

A number of compounds analogous to adrenaline but minus the hydroxyl of the secondary alcoholic group have been synthesized. The three following syntheses are typical:

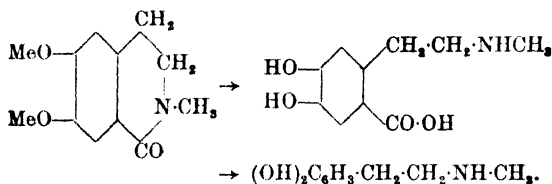
(1) **Epinine**, 3:4-dihydroxyphenylethylamine,  $(\text{OH})_2\text{C}_6\text{H}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$  (*Mannich and Jacobsohn*, B., 1910, 189):



It can also be obtained from the alkaloids laudanosine and papaverine (Chap. LVIII, D.) by oxidation.

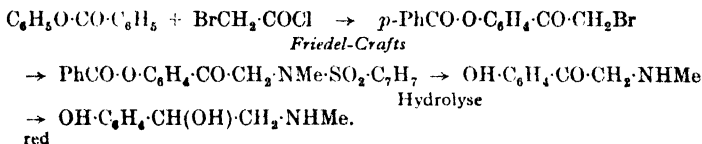
(2) 3:4-dihydroxyphenylethyl-methylamine,  $(\text{OH})_2\text{C}_6\text{H}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CH}_3$  (*Pyman*, J. C. S., 1910, 264), from 1-keto-

6 : 7-dimethoxy-2-methyl-tetrahydroisoquinoline and hydrochloric acid at 170°-175°:



The methyl groups are removed, the ring is broken between the carbonyl group and nitrogen atom by the addition of water, and finally carbon dioxide is eliminated.

(3) **Sympathol** (*synephrin*), 2-*p*-hydroxyphenyl-2-hydroxyethyl-methylamine,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{NHMe}$ , prepared from phenyl benzoate and bromoacetyl chloride by the following stages:



(4) **Hordenine**, *p*-hydroxyphenylethyl-dimethylamine, a substance present in germinating barley, from phenylethyl alcohol (*Barger*, J. C. S., 1909, 2193). Hordenine is now made by methylating *p*-hydroxyphenylethylamine with methyl chloride.

*Barger* and *Dale* (J. physiol. 1910, **41**, 19) have made a careful comparison of the physiological properties of these and numerous similar compounds. Some of the conclusions they arrived at are:

1. The sympathomimetic action is characteristic of a large series of amines, the simplest being the primary aliphatic amines.

2. As the structure of the amine approaches that of adrenaline the activity increases. The optimum effect is attained with a carbon skeleton consisting of a benzene ring with a side chain of two carbon atoms, the terminal one bearing the amino group. Another condition for optimum effects is the presence of two phenolic hydroxyl groups in the positions 3 : 4 relative to the side chain. When these are present an

alcoholic hydroxyl still further intensifies the activity. A phenolic hydroxyl in position 2 has no effect.

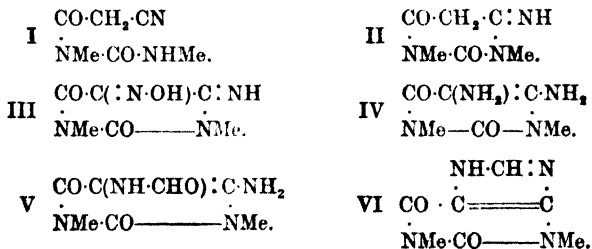
3. The quaternary ammonium salts corresponding with the amines related to adrenaline and tyramine have an action similar to that of nicotine.

### E. Excitants

Used for increasing blood pressure and as cerebral stimulants. **Caffeine** is frequently used with antipyrin or aspirin; it also has a diuretic action. **Camphor** is also used, and hexeton, 1-methyl-5-isopropyl-3-keto- $\Delta^1$ -cyclohexene, is stronger than camphor.

### F. Diuretics and Uric Acid Eliminants and Various Drugs

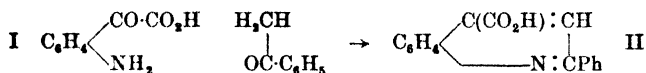
Most purine derivatives have diuretic action. The best known of these is caffeine (p. 331), but its chief use in medicine is as an excitant, with, e.g., aspirin. The most powerful diuretic of the group is theophylline, 1:3-dimethylxanthine (p. 331), and is manufactured by *Traube's* synthetical method (B., 1900, 3053). *s*-Dimethylcarbamide and cyanoacetic acid condense in the presence of phosphorus oxychloride yielding (I), which is transformed by alkali into the cyclic base (II). This base yields an isonitroso compound (III), which can be reduced to the corresponding diamine (IV) by means of ammonium sulphide. The diamine with formic acid yields a formyl derivative (V), which gives theophylline (VI) when heated with alkali.



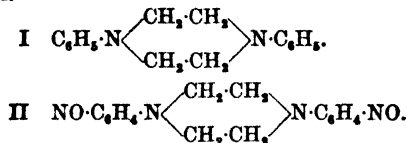
Theobromine has similar properties, and both are devoid of the excitant properties of caffeine.

Numerous remedies for gout have been suggested; these are either recommended with the idea of preventing the formation of uric acid or of dissolving it when formed and eliminating it from the system. Compounds of the first type are relatively complex acids, e.g. quinic acid from coffee beans (p. 529), diphenyl tartrate, hippuric acid (p. 517), salicylic acid derivatives.

**Atophan**, 2-phenylquinoline-4-carboxylic acid ( $N = 1$ ), is largely used in cases of gout. Similar compounds with  $\text{CO}_2\text{H}$  or  $\text{OH}$  in the benzene ring or with  $\text{Ph}$  in 3 or  $\text{CO}_2\text{H}$  in 2 and  $\text{Ph}$  in 4 are valueless. The methyl ester (**novatophan**) and allyl ester (**atochinol**) are even more effective, and the urethane ( $\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}_2\text{Et}$  in place of  $\cdot\text{CO}\cdot\text{OH}$ ) **fantan** has antirheumatic and antineuralgic effects. **Hexophan** has  $\cdot\text{C}_6\text{H}_3(\text{OH})\text{CO}_2\text{H}$  in place of  $\text{Ph}$  in position 2. Atophan is best prepared from isatin, which with alkali reacts as the *o*-amino acid (I), and this with acetophenone loses  $2\text{H}_2\text{O}$  yielding atophan (II):



Of uric acid solvents, **piperazine**, the reduction product of pyrazine (Chap. XLV, A.), was first obtained by *Hofmann* by the action of ammonia on ethylene dichloride or dibromide, and is most readily purified by means of its di-nitroso derivative, which yields the base when treated with hydrochloric acid or reducing agents. Another method is from ethylene dibromide and aniline. The product is diphenyl-piperazine (I); this with nitrous acid yields a di-nitroso derivative (II), which is hydrolysed by caustic soda to piperazine and *p*-nitrosophenol.



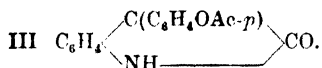
Various salts of piperazine are also used, e.g. piperazine quinate is **urol** or **sidonal**, and the tartrate of dimethylpiperazine is **lysetol**. The compound  $\begin{matrix} \text{CH}_2\cdot\text{N} \\ | \\ \text{CH}_2\cdot\text{NH} \end{matrix} \begin{matrix} \diagup \\ \diagdown \end{matrix} \text{C}\cdot\text{CH}_3$ , **lysidine**, has a solvent action eight times as great as that of piperazine.

Numerous hexamethylenetetramine derivatives have also been recommended as uric acid eliminants.

### G. Laxatives

Many of the milder natural purgatives, such as cascara, senna, aloes, and rhubarb, appear to contain hydroxy derivatives of anthraquinone (p. 583) as their active constituents, and a number of synthetic hydroxy derivatives of anthraquinone have been investigated. Of these the most active is anthrapurpurin or the 1:2:7-trihydroxy derivative; also the 1:8-dihydroxy (chrysarin). Phenolphthalein is also used as a purgative.

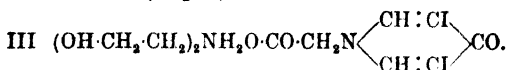
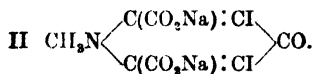
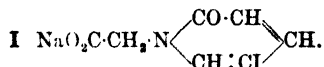
**Isacen** (III) from isatin, phenol and concentrated sulphuric acid, and the product acetylated is a good laxative:



Certain derivatives of aloin, the active principle of aloes, have been prepared and used, e.g. the condensation product of aloin with formaldehyde and tribromoaloin and triacetylaloin.

### H. Skiagraphic Chemicals

Certain derivatives of 2- and 4-pyridones are used as intravenous injections for rendering certain tissues, especially nerves and arteries, opaque to X-rays, and are of great value in X-ray examination of the human body. These are **uroselectan** (I), **uroselectan B** (II), and **perabrodil** (III).



No. II is obtained from chelidonic acid (p. 680) by replacing O by NH, methylating and iodinating.

The sodium derivative of tetraiodophenolphthalein (four I ortho to two OH) is used for radiological examination of the gall bladder.

## I. Synthetic Alkaloids

### 1. ANTIMALARIALS (*Henry*, J. S. C. I., 1936, 111 T.)

Attention has already (p. 1005) been drawn to the various esters of quinine which are used instead of the natural alkaloid, as they are free from the bitter taste of the latter. These esters are much more expensive than quinine, and are not so generally used. The absence of bitter taste is largely due to their insolubility, and in the organism they are hydrolysed to quinine and the corresponding acid. Euquinine is manufactured by the action of ethyl chloroformate,  $\text{Cl}\cdot\text{CO}_2\text{C}_2\text{H}_5$ , on quinine.

Various ethers have also been examined (C. and I., 1937, 1114). There is first an increase in activity and then a decrease as the number of C atoms increases. The esters of **quitenine**, the carboxylic acid obtained by oxidizing the vinyl group of quinine, more particularly the *n*-butyl and *n*-amyl compounds, are efficient antimalarials.

The synthetic **plasmoquine**, 8-diethylamino-*iso*-amylamino-6-methoxyquinoline, i.e. with the  $\text{NEt}_2(\text{CH}_2)_3\cdot\text{CHMe}\cdot\text{NH}\cdot$  group in position 8, is used as a quinine substitute. The same long side chain occurs in **atebrin**, a 2-chloromethoxy derivative of acridine with the long side chain attached to the C atom of the central ring; it is used in the form of the methyl sulphonate for treatment of malaria.

Numerous quinoline derivatives have been examined, viz. those containing Me, OH, OMe, OEt, OPr in position 6 and  $\cdot\text{NH}(\text{CH}_2)_n\cdot\text{NEt}_2$  in 8, where *n* varies from 2 to 11 and the compound with  $\cdot\text{NH}(\text{CH}_2)_3\cdot\text{NEt}_2$  is 2.5 times as effective as plasmoquine, and replacing  $\text{NEt}_2$  by  $\text{NH}_2$  or  $\text{NHPr}$  or  $\text{NHBu}$  lessens the activity.

### 2. AMŒBACIDES

The alkaloid emetine from ipecacuanha is the common drug, but the synthetic **Tadd**, 1:10-tetra-*n*-amylldiaminodecane,  $(\text{C}_5\text{H}_{11})_2\text{N}\cdot[\text{CH}_2]_{10}\text{N}(\text{C}_5\text{H}_{11})_2$ , is more efficient and only 0.1 as toxic as emetine (C. and I., 1937, 793). It is far and away



the most effective of the compounds  $R_2N(CH_2)_nNR_2$  or  $R_2N(CH_2)_nNH_2$ .

### 3. SYNTHETIC TROPEINES

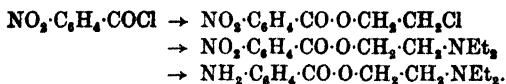
**Homatropine** (Chap. LVIII, J.), the tropine ester of mandelic acid,  $C_6H_5 \cdot CH(OH) \cdot CO \cdot OC_8H_{14}N$ , is prepared on the large scale from its components, and is used as a substitute for atropine, as it is less toxic and its mydriatic action develops and passes off more readily.

### 4. LOCAL ANÆSTHETICS

The simplest local anæsthetics belong to the group of amino-benzoic esters. **New orthoform** is methyl 3-amino-4-hydroxybenzoate,  $OH \cdot C_6H_3(NH_2) \cdot CO_2Me$ , and is prepared from *p*-hydroxybenzoic by esterification, nitration and reduction. The *p*-hydroxy acid is prepared by Kolbe's synthetical method at  $200^\circ$ – $220^\circ$  (Chap. XXVI, A3). It paralyses nerve endings and can be used as a mild antiseptic for dusting wounds. **Anesthesin**, ethyl *p*-aminobenzoate, has only a mild action; its salt with *p*-phenolsulphonic acid is used for hypodermic injections under the name **subcutin**. **Nirvanine** is the dimethyl-glycyl derivate of methyl 2-hydroxy-5-aminobenzoate,  $NMe_2 \cdot CH_2 \cdot CO \cdot NH \cdot C_6H_3(OH) \cdot CO_2Me$ .

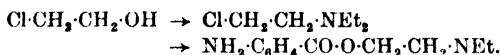
**Butesin** is *n*-butyl *p*-aminobenzoate. **Butyn** is the sulphate of *n*-3-dibutylaminoethyl *p*-aminobenzoate,  $NH_2 \cdot C_6H_4 \cdot CO \cdot O \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot N(C_4H_9)_2$ , and **spinocain** is  $C_4H_9NH \cdot C_6H_4 \cdot CO \cdot O \cdot CH_2 \cdot CH_2 \cdot NMe_2$ ,  $\beta$ -dimethylaminoethyl butylaminobenzoate. **Novocaine**, the hydrochloride of diethylaminoethyl *p*-aminobenzoate,  $NH_2 \cdot C_6H_4 \cdot CO \cdot O \cdot CH_2 \cdot CH_2 \cdot NEt_2 \cdot HCl$ , is a common local anæsthetic, as it is non-irritant and only about one-seventh as toxic as cocaine. The following synthetic methods are used for its preparation:

1. Condensation of *p*-nitrobenzoyl chloride with ethylene chlorhydrin, heating the product with diethylamine at  $100^\circ$ – $120^\circ$ , and reducing the nitro group by means of tin and hydrochloric acid:



2. Ethylene chlorhydrin and diethylamine are condensed to

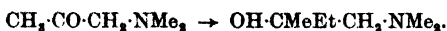
form chlorethyldiethylamine, which is then heated with sodium *p*-aminobenzoate:



3. *p*-Aminobenzoic acid is condensed with ethylene chlorhydrin at 100° in sulphuric acid solution, and the product then heated with diethylamine at 100°–110°, or alternatively  $\beta$ -bromoethyl *p*-nitrobenzoate is synthesized from sodium *p*-nitrobenzoate and ethylene bromide, and this is then condensed with diethylamine and the nitro group in the resulting product reduced.

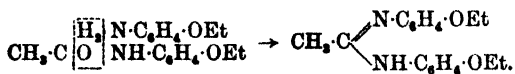
By lengthening the chain of the ester group the anæsthetic properties are augmented, but so also are the toxic properties. **Tutocaine** with the ester group,  $\text{CO}\cdot\text{O}\cdot\text{CHMe}\cdot\text{CHMe}\cdot\text{CH}_2\cdot\text{NMe}_2$ , is almost twice as toxic as novocaine. **Pantocaine**,  $\beta$ -dimethyl-aminoethyl 4-butylamino-benzoate,  $\text{CH}_3(\text{CH}_2)_3\cdot\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NMe}_2$ , is 10 times as effective as novocaine.

**Stovaine**, methyl-ethyl-dimethylaminomethyl-carbinyl benzoate,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{O}\cdot\text{CMeEt}\cdot\text{CH}_2\cdot\text{NMe}_2$ , HCl, is a well-known anæsthetic, and is a representative of the group of compounds known as alkamine esters, which contain the grouping  $\text{R}\cdot\text{CO}\cdot\text{O}\cdot\text{C}\cdot\text{C}\cdot\text{NR}$ . It is synthesized by the action of magnesium ethyl bromide on dimethyl-amino-acetone and benzylation of the product



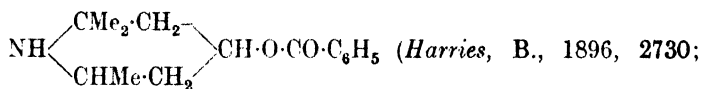
**Alypine** is the corresponding tetramethyldiamino-di-methyl-ethyl-carbinyl benzoate,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{O}\cdot\text{C}(\text{CH}_2\text{NMe}_2)_2$ .

**Holocaine**, the hydrochloride of  $\text{CH}_3\cdot\text{C} \begin{array}{l} \nearrow \text{N}\cdot\text{C}_6\text{H}_4\cdot\text{OEt} \\ \searrow \text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{OEt} \end{array}$ , is used in ophthalmic surgery, and is manufactured by condensing phenetidine (p. 481) with its acetyl derivative phenacetine:

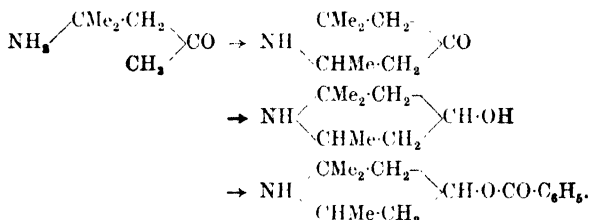


It is sparingly soluble, and its solutions keep well, but it has toxic properties.

**$\beta$ -Eucaine**, benzoylvinyldiacetone-alkamine hydrochloride,



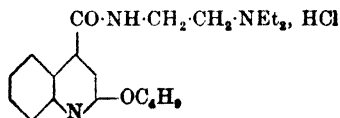
A., 1897, **294**, 372; **296**, 328; 1898, **299**, 346), it can be synthesized by the following series of reactions: Acetone and ammonia yield diacetonamine (p. 159), which condenses with aldehyde, yielding the cyclic 2:2:6-trimethyl-4-ketopiperidine; this can be reduced to the corresponding secondary alcohol by sodium amalgam, and then benzoylated:



Certain aromatic ethers are also used as local anæsthetics. **Acoin**,  $\text{OMe} \cdot \text{C}_6\text{H}_4 \cdot \text{N} : \text{C}(\text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{OMe})_2$ , is a guanidine derivative (Chap. XIII, E.) and is formed from  $\text{CS}_2$ , and anisidine followed by the action of  $\text{PbO}$  and more anisidine. The analogous **diocaine** is a diallyl ether,



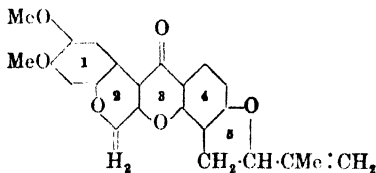
**Percaine**, which is 10 times as active as cocaine and can be used in combination with adrenaline, is a quinoline derivative, viz. 2-butoxy-quinoline-4-carboxamide with the  $\beta$ -diethylaminoethyl group attached to NH.



It is synthesized as follows: 2-quinolone-4-carboxylic acid, obtained by heating isatin and malonic acid with fused sodium acetate, is converted into the acid chloride of 2-chloroquinoline-4-carboxylic acid, which with bromoethylamine gives a side chain  $\cdot \text{CO} \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{Br}$ . By the action of  $\text{NHEt}_2$  the chain  $\cdot \text{CO} \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{NEt}_2$  is formed, and then by treating with sodium *n*-butyl oxide the Cl at 2 is replaced by  $\text{OC}_4\text{H}_9$ .

## J. Insecticides

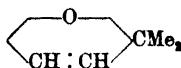
**Rotenone** (Chem. Rev., 1933, 81)



is one of the principles of derris root (*Derris elliptica*) and also of *Lonchocarpus nicou*, the former of which is largely used as an insecticide and as a fish poison. Dihydrorotenone formed by addition of 2H to the benzfuran ring is more stable than rotenone and has greater insectidal activity.

Other active components are:

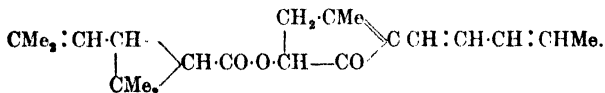
(1) **Deguelin**, similar to rotenone, but with ring 5 in form of a pyrane ring,



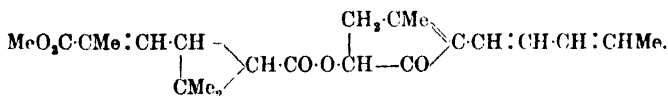
(2) **Toxicarol** (hydroxydeguelin) with OH in ring 4 para to  $\text{CH}_2$ .

Pyrethrum (*Chrysanthemum cinerariaefolium*) is a common insecticide and contains the active principles pyrethrin I and pyrethrin II (Standinger and Ruzicka, Helv., 1924, 177; La Forge and Haller, J. A. C. S., 1936, 1061, 1777).

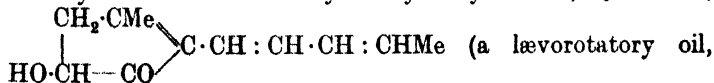
### Pyrethrin I



### Pyrethrin II



They are esters of the cyclic hydroxy ketone, **Pyrethlone**,



(a laevorotatory oil,

b.-pt.  $111^{\circ}$ – $112^{\circ}$ /0.05 mm.), with chrysanthemum mono- and di-carboxylic acids. The monobasic acid is an oil, b.-pt.  $135^{\circ}$ /12 mm. and volatile with steam, and the dibasic acid a solid, m.-pt.  $164^{\circ}$  and non-volatile with steam.

Nicotine (Chap. LVIII, B.) is the commonest insecticide, and the *r*-compound is less active than the *l*. Dipyrindyl, piperidylpyridine, and dipiperidine are also toxic to insects.

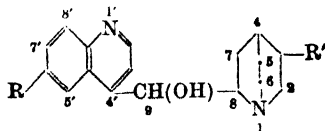
Esters of thiocyanic acid also have high toxicity, e.g. lauryl thiocyanate. Allyl thiocarbamide is a powerful insecticide, also trimethylene dithiocyanate,  $\text{CNS}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CNS}$ , and phenyl- $\gamma$ -thiocyano-propyl ether,  $\text{OPh}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CNS}$ . In the group of alkyl thiocyanates a rise in toxic value is observed as the number of carbons increases to 12 and then begins to fall as the number increases.

## K. Constitution and Physiological Activity

The production of a large number of new synthetic drugs has led to the study of the relationship between chemical constitution and physiological action or therapeutic effect. Numerous generalizations have been drawn, but, as a rule, these only hold within very narrow limits (cf. previous sections), and it may be stated that, on the whole, the relationships between chemical constitution and physiological activity still remain obscure.

A large number of derivatives of quinine (Chap. LVIII, C.) have been prepared, and their activity as antimalarials studied (Chem. Rev., 1942, 49).

The quinine skeleton is represented as



In both quinine and quinidine  $\text{R} = \text{OCH}_3$ ; in cinchonine and cinchonidine  $\text{R} = \text{H}$ , and in cupreine  $\text{R} = \text{OH}$ . In all five  $\text{R}' = \cdot\text{CH}\cdot\text{CH}_3$ .

In the hydro-bases the vinyl becomes ethyl, and in alkyl cupreins OH becomes Oalk. There are four centres of dissymmetry in the molecule, viz. 3, 4, 8 and 9, and hence numerous stereoisomerides are possible. The chief products have been

obtained by hydrogenating the vinyl group or by introducing various alkyloxy groups in place of the OMe at 7'. Dihydroquinine is physiologically more active than quinine and ethylidene in place of vinyl increases the activity. An increase in the number of C atoms in the alkyl group first raises the activity but afterwards diminishes it. The  $\cdot\text{CH}(\text{OH})\cdot$  group at 9 appears to be indispensable as when this becomes  $\cdot\text{CHCl}\cdot$ ,  $\text{CH}_2\cdot$ ,  $\cdot\text{CO}\cdot$  or  $\cdot\text{CH}(\text{OAc})\cdot$ , the activity disappears. Epimerization at No. 9 also produces a less active product. The oxidation product, quinetine (carboxylic acid  $\text{CO}_2\text{H}$  in place of vinyl), is physiologically inactive, whereas its esters show activity.

The introduction of a sulphonic acid group into the molecule of a physiologically active substance usually reduces the activity; thus the sodium salts of phenolsulphonic acid and morphine-sulphonic acid are devoid of the activity characteristic of the parent substances. A carboxyl group has much the same effect, but if the carboxyl group is esterified the product frequently regains its toxic properties. The acetyl group often produces a diminution in toxic properties, as shown by a comparison of aniline and acetanilide.

An increase in toxicity and physiological activity is frequently produced by reducing a cyclic system containing nitrogen, as shown by a comparison of pyrrole, pyridine, and  $\beta$ -naphthylamine with pyrrolidine, piperidine, and tetrahydro- $\beta$ -naphthylamine.

Nearly all amines, including alkaloids, when converted into quaternary ammonium salts lose their characteristic physiological effects, and become strong paralyzers of motor nerve endings. Similar physiological effects are produced by phosphonium, arsonium, and sulphonium salts. An increase in the number of olefine linkings frequently produces marked physiological effects. This is shown by a comparison of allyl with propyl alcohol and of carvone with the saturated analogue menthone. In both cases the unsaturated compound has greater physiological activity.

The introduction of hydroxyl groups into the benzene ring increases the activity, whereas in the aliphatic series the introduction of such groups diminishes activity, as shown by a comparison of the inert sugars with the toxic simple aldehydes.

The aliphyl nitrites tend to produce a dilatation of the blood-vessels or to lower the blood pressure. This property

is most marked with amyl nitrite and least with the methyl compound. A similar property is characteristic of certain nitrates, particularly glyceryl trinitrate and erythryl tetra-nitrate, which are largely used in medicine. The aliphatic nitro-compounds, which are isomeric with the nitrites, are strong poisons and do not reduce blood pressure.

Optical isomerides do not necessarily possess the same degree of physiological activity; thus atropine is intermediate in activity between the *d*- and *l*-hyoscyamines, which exhibit markedly different properties; *l*-nicotine is twice as poisonous as *d*-nicotine, and the two asparagines (p. 284) have different tastes.

The fate of drugs in the organism has received much attention. As a rule substances which are extremely readily decomposed, or substances which pass through the system quite unaltered, are of little value as drugs. The main changes which occur in the organism are (a) hydrolysis, (b) oxidation, (c) reduction. Hydrolysis can be due to the slightly acid stomach juices containing pepsin, or, in the case of esters, to the slightly alkaline juices of the small intestine, which contain the pancreatic enzyme lipase. One of the objects of synthesizing new products is to obtain substances which can pass the stomach without undergoing hydrolysis, but which are readily hydrolysed in the small intestine, yielding products which can then exert their specific action.

Oxidation frequently takes place, more particularly in the tissues or blood. Many aliphatic compounds are oxidized to carbon dioxide, water, and urea; others to acids. Many aliphatic compounds containing methyl groups or halogen are not readily oxidized. With aromatic compounds containing side chains the side chain is usually oxidized, but the benzene ring left intact. Compounds of the type  $C_6H_5 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$  are completely oxidized. Another type of oxidation is the formation of phenolic hydroxy groups, e.g. aniline yields *p*-aminophenol. Reduction also takes place in the blood and tissues, but is not so common as oxidation. Nitrobenzaldehydes can give rise to aminobenzoic acids and picric acid to dinitroamino-phenol.

As a rule the primary products of change, if they are toxic, are not excreted as such, but in the form of compounds with sulphuric acid or glycuronic acid,  $CHO \cdot (CH \cdot OH)_4 \cdot CO_2H$ . Thus phenol always forms sodium phenyl sulphate,  $SO_3(ONa)OPh$ ,

a non-toxic substance. Salicylic and benzoic acids are partly eliminated in the form of derivatives with glycine, i.e. in the form of compounds of the hippuric acid type.

## LXVI. ORGANIC DERIVATIVES OF ARSENIC

In studying the various groups of carbon compounds, attention has already (pp. 97, 131, 132) been drawn to the fact that elements belonging to the same group in the periodic classification tend to give rise to similar types of organic derivatives.

Nitrogen, phosphorus, and arsenic belong to the same group, and hence the derivatives of arsenic should resemble those of nitrogen. Attention has already been drawn to such resemblances in the case of the arsines and arsonium compounds. The compound **pentamethylarsine**,  $\text{AsMe}_5$ , was described by *Cahours* in 1862 as an oily liquid, and it is only recently that analogous nitrogen compounds have been prepared by *Schlenk* and *Holtz* (Ber., 1916, **49**, 605; 1917, **50**, 274); for example, **benzyltetramethyl-ammonium**,  $\text{NMe}_4 \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$  (cf. p. 442).

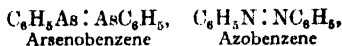
The chief groups of nitrogen compounds may be tabulated as follows:

- (a) Amines and alkylated ammonium salts.
- (b) Nitroso- and nitro-derivatives.
- (c) Azo- and diazo-compounds.
- (d) Nitriles and acid amides.
- (e) Cyclic compounds with the nitrogen atom forming part of the ring.

So far arsenic derivatives corresponding with nitriles and acid amides have not been isolated.

The arsine oxides are analogous to the nitroso-compounds, e.g. phenylarsine oxide,  $\text{C}_6\text{H}_5 \cdot \text{As} : \text{O}$ , to nitrosobenzene, and *p*-hydroxyphenyl-arsine oxide,  $\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{AsO}$ , to *p*-nitrosophenol.

The arseno-compounds are analogous to the azo-compounds,





and are at the present time compounds of commercial importance, as some of their derivatives find use as drugs (see Salvarsan). Aliphatic arseno-compounds of the type of arsenoethane,  $C_2H_5As:AsC_2H_5$  (*Auger*, C. R., 1904, 138, 1705), have also been prepared.

Arseno-methane, however, is  $(AsMe)_5$ , a ring of 5 As atoms with a methyl group attached to each.

### A. Arylarsonic Acids

The arylarsonic acids,  $R \cdot As \begin{smallmatrix} \nearrow O \\ \searrow (OH)_2 \end{smallmatrix}$ , comprise a group of

great technical importance, as some of the substituted arsonic acids give rise to derivatives which possess considerable therapeutic value. Phenylarsonic acid,  $C_6H_5 \cdot As(OH)_2:O$ , may be regarded as the hydrate of the arsenic analogue of nitrobenzene, and, when it is warmed, water is eliminated and the

anhydride,  $R \cdot As \begin{smallmatrix} \nearrow O \\ \searrow O \end{smallmatrix}$ , is formed. The main difference between

the nitrogen and arsenic compounds is that in the nitrogen series the anhydrides,  $R \cdot NO_2$ , are the stable compounds, the hydrates being unknown, whereas in the arsenic series the hydrates,  $R \cdot AsO(OH)_2$ , are the important compounds.

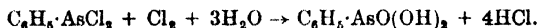
The arylarsonic acids are well-defined crystalline substances, and in the majority of them the arsonic acid group is firmly attached to the benzene ring, so that the compounds may be used in a variety of different ways for synthetic purposes (*Ehrlich*). When reduced they can yield arsine oxides,  $R \cdot As:O$ , arseno-compounds,  $RAs:AsR$ , or even primary arsines,  $RAsH_2$ , and thus resemble the nitro-compounds. They possess distinct acidic properties, yield soluble alkali salts and insoluble salts of heavy metals, but do not give precipitates with magnesia mixture in the cold; when heated, however, insoluble magnesium salts free from ammonia are formed.

A common synthesis of arsonic acids is by the action of arsenious acid or its salts on diazonium salts:



The best yields are obtained when the salt  $K_2HASO_3$  is used (*Schmidt*, A., 1920, 421, 159).

Another method of formation is by the combined action of chlorine and water on chloroarsines (p. 135) (B., 1894, 265):

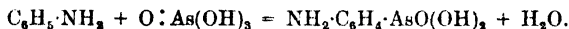


A convenient method for preparing phenylarsonic acid itself is by the elimination of the amino-group from *p*-amino-phenylarsonic acid (Bertheim, B., 1908, 1855).

The esters of the arsonic acids can be prepared from the silver salts and alkyl iodides, and are disagreeably smelling liquids, which are readily hydrolysed when brought into contact with water.

The anhydride,  $\text{C}_6\text{H}_5\text{AsO}_2$ , obtained by dehydrating the corresponding acid at  $140^\circ$ , is a white amorphous powder; does not absorb moisture from the air, but dissolves in water yielding the acid.

Amino-derivatives of arylarsonic acids can be obtained by direct synthesis, namely, by heating a primary arylamine with arsenic acid:



In this reaction the  $\cdot\text{AsO}_3\text{H}_2$  group always occupies the para-position with respect to the amino group, unless this position is already filled, when it takes up the ortho-position. A meta-amino-compound can be prepared by nitrating the unsubstituted arsonic acid and reducing the *m*-nitro acid by means of sodium amalgam and methyl alcohol; if other reducing agents are employed the arsonic acid group also is reduced.

***p*-Aminophenylarsonic acid**,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{AsO}_3\text{H}_2$ , is formed when aniline arsenate is heated. The process is usually termed **arsenating**—analogous to **sulphonating**—and the product is known as **arsanilic acid** (Ehrlich and Bertheim, B., 1907, 3292; Benda, 1908, 1674; 1909, 3621; Kober and Davis, J. A. C. S., 1919, 451). The reaction proceeds best at a temperature of  $160^\circ$ – $185^\circ$  and in the presence of an excess of aniline (3 mols. : 2 mols. acid), but under no conditions is the yield a theoretical one. The arsenic acid appears to have an oxidizing action on the aniline, and red and black products are formed. A **diaminodiphenylarsonic acid**,  $\text{O}:\text{As}(\text{C}_6\text{H}_4\cdot\text{NH}_2)_2\cdot\text{OH}$ , is also formed as a by-product.

The amino group in these compounds is reactive and can be diazotized with the greatest readiness, and the diazo compounds so formed show the reactions characteristic of aromatic

diazonium salts, including the formation of azo-dyes. The  $\cdot\text{AsO}(\text{OH})_2$  group is, on the whole, firmly united to the benzene ring, but can be readily replaced by iodine when the amino acid is warmed with potassium iodide and dilute sulphuric acid; in a similar manner arsanilic acid with bromine water yields *s*-tribromoaniline, a reaction analogous to that between sulphanilic acid and bromine water. The replacement of the arsonic acid residue by iodine is frequently used for determining the relative positions of the substituents in aminoarylarsonic acids, e.g. *o*-arsanilic acid yields ortho-iodoaniline.\* Free *p*-arsanilic acid is sparingly soluble in water or alcohol, but as an amphoteric substance dissolves readily in dilute mineral acids or alkalis. The mono-sodium salt was introduced into medicine in 1902 under the name of **Atoxyl**, and was the first aryl derivative of arsenic to find a therapeutic use; the well-defined crystalline salt,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{AsO}(\text{OH})(\text{ONa})\cdot 5\text{H}_2\text{O}$ , is the drug **Soamin**. The stability of arsanilic acid towards sodium hydroxide solution at  $100^\circ\text{--}130^\circ$  is interesting. With 1.5 mols. of alkali to one of the acid the solution is quite stable, and no hydrolysing action occurs; the maximum hydrolysis takes place when the ratio is 0.8 : 1. The replacement of the hydrogen atom of the second hydroxyl group thus has a stabilizing effect, and a similar result is obtained by acylating the amino group; the conclusion is drawn that the cause of instability is due to some interaction between the amino group and the second hydroxyl group (*Schmitz*, B., 1914, 363). For several years atoxyl was used in the form of intravenous injections in cases of anæmia, syphilis, elephantiasis, malaria, and other protozoal diseases, but it is highly toxic and affects the eyes and kidneys, and as its effects are cumulative it has been replaced by the less dangerous derivatives of trivalent arsenic of the salvarsan type (this Chap., B.).

Halogenated arsanilic acids can be obtained by the action of halogens in the absence of water, the halogen taking up the ortho-position relative to the amino group. The mononitro derivative, 3-nitro-4-aminophenylarsonic acid, is best prepared by nitrating the oxalyl or urethane derivative,  $\text{H}_2\text{O}_3\text{As}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{CO}_2\text{H}$  or  $\text{H}_2\text{O}_3\text{As}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CO}\cdot\text{OEt}$ , and when reduced with alkaline hydrosulphite yields the *o*-diamine,

\* Amino acids in which the amino group is in the meta-position relative to the arsonic acid group are not decomposed by halogens or hydriodic acid.

3:4-diaminophenylarsonic acid, which gives most of the reactions characteristic of *o*-diamines (p. 442).

As an amine atoxyl gives rise to a series of acyl derivatives, two of which are *monoacetylatoxyl* (**arsacetin**),  $\text{NHAc} \cdot \text{C}_6\text{H}_4 \cdot \text{AsO}(\text{OH})(\text{ONa})$ ,  $5\text{H}_2\text{O}$ , and *sodium-4-benzenesulphonyl-1-amino-phenylarsonate* (**pectine**),  $\text{SO}_2\text{Ph} \cdot \text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{AsO}(\text{OH})(\text{ONa})$ . Both of these were used at one time in medicine—as they are less toxic and more stable; for example, their solutions can be sterilized by boiling without undergoing decomposition—but have now been discarded.

With aldehydes arsanilic acid yields benzylidene and analogous derivatives, e.g.  $\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{AsO}(\text{OH})_2$ , which are usually coloured and amphoteric in character.

Numerous hydroxy derivatives of arylarsonic acids are known. *p*-**Hydroxyphenylarsonic acid**,  $\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{AsO}(\text{OH})_2$ , obtained by heating phenol with arsenic acid ( $\text{H}_3\text{AsO}_4$ ) at  $150^\circ$  (Conant, J. A. C. S., 1919, 431), or by diazotizing *p*-arsanilic acid and warming the solution, forms a crystalline mass readily soluble in water or alcohol.

**Spirocid**, **acetarsol** or **stovarsol**,  $\text{OH} \cdot \text{C}_6\text{H}_3(\text{NHAc})\text{AsO}_3\text{H}_2$ , (1 : 2 : 4) is used for syphilis, and also its salt with  $\text{OH} \cdot \text{C}_2\text{H}_4 \cdot \text{NH}_2$ , known as **salvarsin**. These compounds are non-colloidal, diffuse readily in the organism, and can be administered *per os*. They are sometimes used in conjunction with emetine for amœbic dysentery.

Compounds obtained by condensing *p*-amino-phenylarsonic acid with amides, ureides or anilides of halogenated fatty acids are also valuable agents in treating trypanosomal and spirochætal infections, e.g. **carbarsone**,  $p\text{-H}_2\text{O}_3\text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{CO} \cdot \text{NH}_2$ , is less toxic than stovarsol and is one of the best agents against amœbæ.

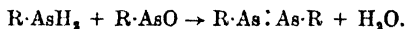
Members of the two groups of amido-compounds I,  $p\text{-H}_2\text{O}_3\text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{NR}'\text{R}''$ , and II,  $p\text{-H}_2\text{O}_3\text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{CO} \cdot (\text{CH}_2)_n \cdot \text{CO} \cdot \text{NR}'\text{R}''$ , have been examined. The general conclusions are: (a) compounds of group I exhibit both trypanocidal and toxic properties; (b) sodium salts of type II are the least toxic of all known arsenicals. Their activity to the trypanosomes of sleeping sickness varies with the value of *n* increasing from *n* = 1 to *n* = 5, and then decreasing. When *n* = 0 (oxalyl series) the compound is highly toxic. **Neoacryl**, sodium succinanilomethylamide-*p*-arsonate,  $\text{Na}_2\text{O}_3\text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{NHMe}$ , is more active than

tryparsamide and can also be used against syphilis (J. C. S., 1931, 615; C. and I., 1937, 853).

**Tryparsamide**, sodium N-phenylglycineamide-*p*-arsonate,  $p\text{-H}_2\text{O}_3\text{As}\cdot\text{C}_6\text{H}_4\cdot\text{NH}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}_2$ , from *p*-arsanilic acid and ethyl chloroacetate and subsequent treatment with ammonia, is also used for treatment of both diseases. A compound as good as or superior to tryparsamide is **orsanine**,  $\text{OH}\cdot\text{C}_6\text{H}_3(\text{AsO}_3\text{H}_2)\cdot\text{NHAc}$  [ $\text{As}:\text{OH}:\text{NHAc} = 1:2:4$ ].

## B. Arsenobenzene Derivatives

As already pointed out, the arseno-derivatives are the arsenic analogues of the azo-compounds, and they can be synthesized by a process analogous to the one described for the azo-compounds (No. 5, Chap. XXII, C3), namely, by condensing a primary arsine with an arsine oxide:



The usual method of preparing arseno-compounds of commercial importance is by the reduction of arylarsonic acids, a reaction similar to the formation of azobenzene by the reduction of nitrobenzene.

In the case of nitro-compounds the actual product obtained depends upon the reducing agent used and the conditions of reduction (pp. 457, 714, 726). A similar statement holds good for the arylarsonic acids. Metals and concentrated acids give rise to primary arsines; mild reducing agents, such as sulphurous acid with a little hydriodic acid, phenylhydrazine or phosphorus trichloride give rise to phenylarsine oxides; whereas sodium hydrosulphite reduces the arsonic acids to arseno-compounds.

The study of the action of reducing agents on compounds containing both nitro and arsonic acid groups has led to some interesting generalizations.

1. Sulphurous acid with hydriodic acid as catalyst, phenylhydrazine, thionyl chloride or phosphorus trichloride give amino-arsine oxides, e.g.  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{As}:\text{O}$ .

2. A metal and strong acid, or electrolytic reduction, especially in the presence of methyl or ethyl alcohol, tends to give rise to amino primary arsines,  $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{AsH}_2$ .

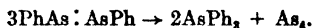
3. Ferrous hydroxide, or the theoretical amount of sodium amalgam, reduces the nitro group but leaves the arsonic acid group intact.

4. Phosphorous and hypophosphorous acids reduce the arsenical group but leave the nitro group intact, and give as products nitro-arylsenso compounds,  $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{As} : \text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{NO}_2$ , and the same result can be effected by stannous chloride activated by hydriodic acid.

5. Sodium hydrosulphite reduces the nitro to an amino group, and the arsonic acid radical to the arseno group, giving rise to the compound  $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{As} : \text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{NH}_2$ .

The arseno group,  $\cdot \text{As} : \text{As} \cdot$ , unlike the azo group,  $\cdot \text{N} : \text{N} \cdot$ , has but feeble chromophoric effect, and the arseno derivatives are, as a rule, pale yellow in colour.

**Arsenobenzene**,  $\text{C}_6\text{H}_5 \cdot \text{As} : \text{As} \cdot \text{C}_6\text{H}_5$ , crystallizes in yellow needles, melts at  $196^\circ$ , and when strongly heated yields triphenylarsine and arsenic:



It is decomposed by chlorine yielding  $\text{C}_6\text{H}_5\text{AsCl}_2$ , by sulphur yielding  $\text{C}_6\text{H}_5\text{AsS}$ , and by oxidizing agents yielding phenylarsonic acid, but with iodine it forms an extremely unstable additive compound,  $\text{C}_6\text{H}_5\text{AsI} \cdot \text{AsIC}_6\text{H}_5$ , in the form of yellow crystals.

Numerous substituted derivatives of arsenobenzene are known, those containing hydroxy and amino, or substituted amino, groups being of greatest technical importance. Characteristic of these compounds is the readiness with which a mixture of two symmetrical arseno-compounds is transformed into an unsymmetrical derivative (Karrer, B., 1916, 1648) by heating to about  $80^\circ$  in the presence of water, e.g.:



Derivatives of arsenobenzene have completely replaced the earlier quinquevalent arsenic compounds used in the treatment of protozoal diseases. They are not only more effective as destroyers of trypanosomes, but are much less toxic, and the possibility of injurious effects on the human body is reduced to a minimum. They are, however, not so effective as compounds of quinquevalent As in cases of syphilis of the nervous system.

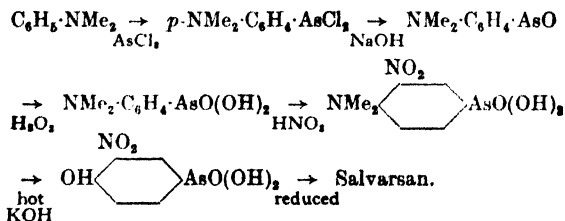
The earliest derivative of therapeutic value was **Salvarsan**, 3:3'-diamino-4 : 4'-dihydroxyarsenobenzene hydrochloride, known also as **Kharsivan**, **Arsphenamine**, or "606".\*

\* It is stated that this compound was termed "606" by Ehrlich, as it was the 606th arsenic compound prepared by him in his attempts to obtain effective remedies for protozoal diseases.

The starting-point for the preparation of salvarsan is *p*-arsanilic acid. This is diazotized in sulphuric acid solution, and the solution of the diazonium salt heated at 70°; the resulting *p*-hydroxyphenylarsonic acid nitrated with a mixture of nitric and sulphuric acids yields 3-nitro-4-hydroxyphenylarsonic acid,  $\text{OH}\cdot\text{C}_6\text{H}_3(\text{NO}_2)\cdot\text{AsO}(\text{OH})_2$  (B., 1911, 3445), the constitution of which follows from the fact that it can be obtained by the diazo-reaction from *o*-nitro-*p*-aminophenol. When the nitro-hydroxy acid is reduced with sodium hydro-sulphite at 55°–60° in the presence of magnesium chloride solution, care being taken that the mixture is well stirred, a microcrystalline, yellow precipitate of the diaminodihydroxy-arsenobenzene is formed.

Salvarsan is made by dissolving the precipitate in methyl alcohol and adding the requisite amount of methyl alcoholic solution of hydrogen chloride. The commercial product containing one molecule of methyl alcohol forms a bulky yellow crystalline powder soluble in most solvents with the exception of acetone, ether or glacial acetic acid. A pure dihydrochloride free from methyl alcohol is colourless (Kober, J. A. C. S., 1919, 442). Like most derivatives of arsenobenzene, salvarsan is readily oxidized in contact with the air, yielding 3-amino-4-hydroxyphenylarsine oxide, which is twenty times as toxic as salvarsan. Iodine or hydrogen peroxide oxidizes salvarsan to the corresponding arsonic acid. Derivatives of salvarsan in which the hydrogen atoms of the hydroxyl groups have been replaced by metallic radicals such as sodium or copper are of therapeutic use.

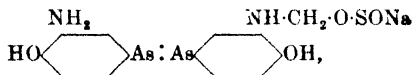
The following is an alternative method for preparing salvarsan:



Numerous alkylated, chloro and nitro derivatives of salvarsan have been prepared, also arsenobenzenes containing as many as six amino groups in the molecule.

One of the chief objections to the use of salvarsan is that its aqueous solutions are distinctly acidic and have to be exactly neutralized with alkali just before intravenous injection.

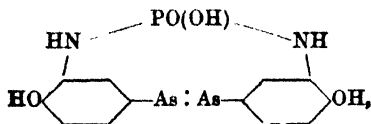
The substance **Neosalvarsan**, known also as **Neokharsivan** or **Neoarsphenamine**, is free from this defect; it is the sodium salt of an N-methylsulphinic acid derived from salvarsan base, and is represented by the structural formula:



sodium 3:3'-diamino-4:4'-dihydroxyarsenobenzene-N-methylene-sulphoxylate, and its aqueous solutions are neutral. Neosalvarsan can be prepared by the action of sodium formaldehyde sulphonylate on salvarsan, precipitating the free acid, dissolving the acid in dilute caustic soda solution, and precipitating the sodium salt by pouring into alcohol. The condensation appears to be facilitated by working in the presence of ethyl alcohol, ethylene glycol, or glycerol. It can also be prepared by the action of a warm aqueous solution of sodium formaldehyde sulphonylate (2 pt.) on sodium 3-nitro-4-hydroxybenzene-arsenate, or by the action of the same reagent on 3:3'-dinitro-4:4'-dihydroxyarsenobenzene.

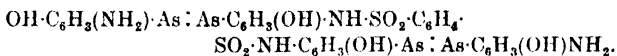
Closely related compounds are **Sulpharsphenamine** or **Sulpharsenol** with  $\cdot\text{CH}_2\cdot\text{O}\cdot\text{SONa}$  attached to each N, and also to the O of OH (*Dyke and King*, J. C. S., 1933, 1003). This can be administered intramuscularly, but a solution must be freshly prepared in sterile water. Compounds which yield stable solutions are (a) **Stabilarsan**, salvarsan-di-N-glucoside, and (b) **Solusalvarsan**, sodium 3:4'-diacetamino-4-hydroxyarsenobenzene-2'-glycollate. All these compounds contain the 3-amino-4-hydroxybenzene residue common to most arsenical antisyphilitics.

Two compounds of the neosalvarsan type which have also been used are: (a) **Galyl**, the sodium salt of 4:4'-dihydroxyarsenobenzene-3:3'-phosphamic acid:



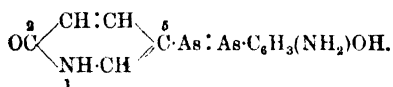


and (b) **Ludyl**, the sodium salt of *benzene-m-3 : 3'-disulphamino-bis-3-amino-4 : 4'-dihydroxyarsenobenzene*:



The former compound is made by condensing 3-amino-4-hydroxy-phenylarsonic acid with phosphorus oxychloride in the presence of aqueous sodium hydroxide solution, and reducing the condensation product with sodium hydrosulphite; and the latter by the condensation of salvarsan with benzene-*m*-disulphonic chloride by the ordinary *Schotten-Baumann* method. Both compounds are only slightly toxic, have energetic spirillicidal action and produce no serious after-effects.

Pyridine analogues of neosalvarsan, i.e. with pyridyl groups in place of phenyl, are of value. One of these is 2-pyridone-5-arseno-3'-amino-4'-hydroxybenzene,



The starting-point for such compounds is 2-pyridone-5-*arsonic acid*, the sodium salt of which is the least toxic of all known arsenical drugs, e.g. 124 parts are comparable with 1 of try-parsamide, and it is largely used. Its isomers and substituted derivatives are also valuable.

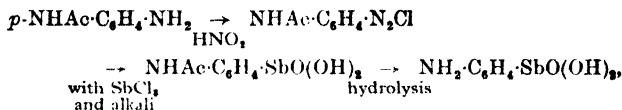
Arsenobenzene and its derivatives form co-ordinated additive compounds with numerous salts of heavy metals, such as copper, silver, gold, mercury, and the platinum metals, e.g.  $\text{RAs}:\text{AsR}$ ,  $\text{MeX}$ , and  $\text{RAs}:\text{AsR}$ ,  $2\text{MeX}$  (*Ehrlich*, B., 1915, 1634).

One of these compounds has been used medicinally, namely **luargol**, or 3 : 3'-*diamino-4 : 4'-dihydroxy-arsenobenzene-silver-bromide-antimonyl-sulphate*  $[\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_2\text{As}_2]_2$ ,  $\text{AgBr}$ ,  $\text{SbO}(\text{H}_2\text{SO}_4)_2$ , an additive compound of salvarsan base with silver bromide and antimonyl sulphate. It is neutralized with caustic soda previous to injection, and is stated to be ten times as active as salvarsan in cases of sleeping sickness.

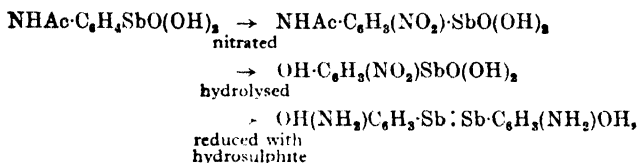
Numerous derivatives of **stibinoarsenobenzene**,  $\text{C}_6\text{H}_5\text{Sb}:\text{AsC}_6\text{H}_5$ , have been prepared, e.g. the 4 : 4'-dihydroxy derivative,  $\text{OH}\cdot\text{C}_6\text{H}_4\text{Sb}:\text{AsC}_6\text{H}_4\cdot\text{OH}$ , is obtained by reducing a mixture of sodium *p*-hydroxyphenylarsonate and *p*-hydroxyphenylstibonate,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{SbO}(\text{ONa})_2$ , with sodium hydrosulphite,

and forms a brownish-black powder insoluble in water. Of this type of compound 3-*amino-4-hydroxyarseno-4'-acetylaminostibinobenzene hydrochloride*,  $\text{HCl} \cdot \text{NH}_2 \cdot \text{C}_6\text{H}_3(\text{OH})\text{As}:\text{SbC}_6\text{H}_4 \cdot \text{NHAc}$ , gives the best therapeutic results.

The antimony analogues of atoxyl and salvarsan are also known, and can be prepared by the following series of reactions:



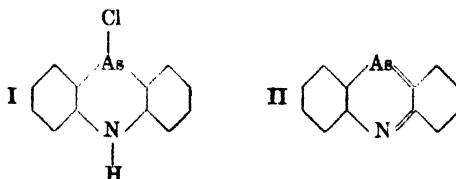
**stibanilic acid**, the antimony analogue of atoxl. The product of these with urea, viz. **ureastibamine**, is largely used in India. The antimony analogue of salvarsan is obtained as follows:



**Sulphoform**, *triphenylstibine sulphide*,  $\text{S}:\text{SbPh}_3$ , colourless needles melting at  $119^\circ\text{--}120^\circ$ , obtained by passing sulphuretted hydrogen cautiously into a solution of triphenylstibine chloride in alcoholic ammonia, is used in pharmacy for curing eczema and similar skin diseases.

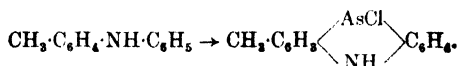
### C. Cyclic Arsenic Compounds

#### Derivatives of 10-chloro-5 : 10-dihydrophenarsazine (I)

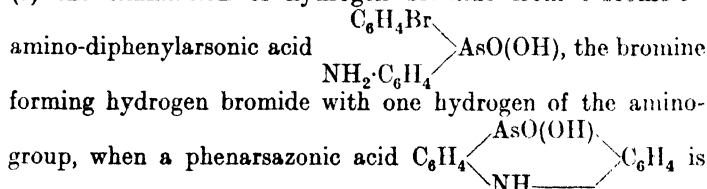


have been prepared by *Gibson* and others (J. C. S., 1926–29; cf. also *Wieland* and *Rheinheimer*, A., 1921, 423, 1) using three different methods.

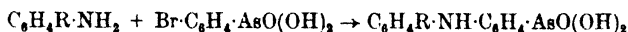
(a) The condensation of arsenious chloride with substituted diphenylamines in suitable solvents, e.g.



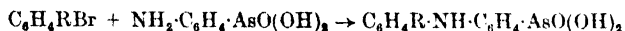
(b) the elimination of hydrogen bromide from *o*-bromo-*o*'-amino-diphenylarsonic acid



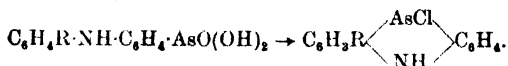
formed; (c) the condensation of *o*-bromo-phenylarsonic acid with substituted amines



or the condensation of *o*-aminophenylarsonic acid with substituted bromobenzenes



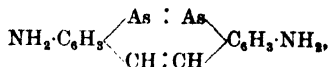
and then ring closure of the product, obtained by either of these condensations, by means of hydrochloric acid, sulphur dioxide and iodine



The compounds are interesting as containing an arsenic atom as part of a ring, and the parent substance, phenarsazine, is represented by formula II.

These cyclic dihydro compounds yield N acyl, but not N alkyl derivatives, and are characterized by the readiness with which they form molecular compounds with acetic acid, acetone, chlorobenzene, carbon tetrachloride, &c.

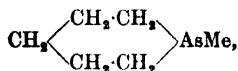
5 : 5'-Diamino-1 : 1'-arseno-2 : 2'-stilbene,



contains an 8-membered ring consisting of six C and two As atoms (*Karrer*, B., 1915, 305). The corresponding arsonic acid is formed from 5-nitro-2-methyl-phenylarsonic acid by the

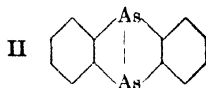
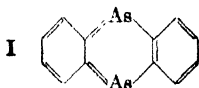
action of caustic soda and subsequent reduction, and on further reduction with hyposulphite yields the ring compound.

An arsenic analogue of N-methyl piperidine is:



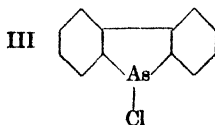
obtained by condensing dichloromethyl-arsine,  $\text{AsMeCl}_2$ , with the magnesium derivative of 1:5-dichloropentane and distilling the product (Bull. Soc., 1916 [iv], **19**, 151, 290). It is termed **1-methylarsepedine**, is a colourless liquid, b.-pt.  $160^\circ$ , with a strong smell of mustard, and is readily oxidized in contact with the air.

Other compounds with two As atoms in the ring are derivatives of **arsanthrene**, viz. I or II, orange rhombic plates, m.-pt.  $340^\circ$ – $350^\circ$ .



The chloride,  $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{AsCl} \\ \diagdown \text{AsCl} \end{array} \text{C}_6\text{H}_4$ , melts at  $182^\circ$ – $183^\circ$ , and

is formed from phenylarsinophenyl-*o*-arsonic acid by reduction with  $\text{SO}_2$  and concentrated hydrochloric acid. The carbazole analogue, III, xylene-2:2'-chloroarsine, is obtained from



the *o*-arsonic acid of diphenyl,  $\text{C}_6\text{H}_5 \cdot \text{C}_6\text{H}_4 \cdot \text{AsO}_3\text{H}_2$ .

Corresponding antimony compounds are known.

## LXVII. PROTEINS: BIOCHEMISTRY \*

An extended description of the substances (other than those already mentioned) which are found in the animal organism, and which are therefore of importance for biochemistry, will not be attempted here, since these and the chemical processes developed in the living tissues form the subject matter of Biochemistry.

## A. Proteins

The proteins constitute the chief part of the organism, being present partly in the colloidal and partly in the solid state; they are found in protoplasm and in all the nutritive fluids of the body. In the tissues of green plants the proteins are synthesized in quite unknown ways from simple substances like carbon dioxide, water, ammonium nitrate and sulphate (cf. *Meldola*, J. C. S., 1906, 749). The majority of proteins are insoluble in water, but dissolve in dilute saline solutions. Their presence in the juices of the animal organism is probably due to saline and other substances. In solution they are opalescent, lævo-rotatory, and do not diffuse through parchment paper, i.e. are colloids; but they are thrown down when the solution is warmed, or upon the addition of strong mineral acids, of many metallic salts [e.g. copper sulphate, basic lead acetate, and mercuric chloride], of alcohol, tannic acid, acetic acid together with a little potassium ferrocyanide, picric acid, or phosphotungstic acid. They are insoluble in alcohol or ether, and their solutions are usually precipitated ("salted out") by the addition of ammonium sulphate, and mixtures of different proteins can often be fractionally precipitated by gradually increasing the concentration of the ammonium sulphate. This concentration is definite for each protein, as is also its temperature of coagulation. Proteins can also be coagulated by treatment with absolute alcohol or with boiling water. After coagulation all proteins become insoluble in neutral solvents, but dissolve in alkalis or acids,

\* *Jordan Lloyd and Shore, Protein Chemistry*, 2nd Edition, London, 1938. *Schmidt, The Chemistry of Amino Acids and Proteins*, Springfield, 1938. *Holmes, The Metabolism of Living Tissues*, Cambridge, 1937. *Plimmer, Organic and Biochemistry*.

yielding **metaproteins**, which are also formed by boiling the uncoagulated protein with acetic acid or alkali. When boiled: (a) with nitric acid, they are coloured yellow (the xanthoprotein reactions); (b) with a solution of mercuric nitrate containing nitrous acid (*Millon's reagent*), red; (c) with caustic soda solution and a very little cupric sulphate, violet.

Some of the proteins have been prepared pure, although this is a very difficult operation.

The different proteins vary only slightly among themselves in percentage composition; they contain:

C = 52.7 to 54.5 p.c.; H = 6.9 to 7.3 p.c.; N = 15.4 to 17.6 p.c.;

O = 20.9 to 23.5 p.c.; and S = 0.8 to 5.0 p.c.

A few proteins have been obtained crystalline, e.g. hemp albumin, ovalbumin, serum albumin. Most are typical colloids and yield colloidal solutions unless broken down. They are amphoteric, i.e. capable of yielding complex cations and anions, depending on the  $p_H$  of the solution. A protein may be regarded as a complex attached to an amino and a carboxyl group, e.g.  $\text{NH}_2 \cdot \text{X} \cdot \text{CO}_2\text{H}$ , and can give rise to ions  $\text{NH}_3^+ \cdot \text{X} \cdot \text{CO}_2\text{H}$  and  $\text{NH}_2 \cdot \text{X} \cdot \text{CO}_2^-$ . Thus gelatin combines with cations when the  $p_H$  is above 4.7 and with anions below 4.7.

Similarly protein particles in alkaline solution in an electric field migrate to the anode, but in acid solution to the cathode. In a solution of  $p_H = 4.7$ , the isoelectric point, the particles show no appreciable movement, probably due to the formation of an inner salt  $\text{NH}_3^+ \cdot \text{X} \cdot \text{CO}_2^-$  or zwitter ion, when the acid and base combining capacity of the protein is at its lowest (cf. Betaines).

The fact that albumin contains sulphur is worthy of note, though the mode in which it is combined in the molecule is unknown; warming with a dilute alkaline solution is sufficient to eliminate it partially, e.g. when white of egg is boiled with an alkaline solution of lead oxide, sulphide of lead is precipitated (the test for sulphur in albumin).

Protein preparations often leave a very considerable amount of ash, i.e. inorganic salts, on incineration. It is not yet certain in how far this mineral matter forms an integral constituent of these substances; but the properties of "egg albumin free from ash" are materially different from those of ordinary albumin.

Although the constitution of no single albumin has been determined, a considerable amount of work has been done in this direction, more especially by an examination of the simpler products obtained when the albumins are (a) oxidized, (b) hydrolysed, and (c) fermented by micro-organisms.

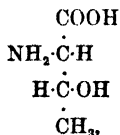
(a) The products obtained on oxidation consist largely of volatile fatty acids, their aldehydes, ketones, and nitriles, together with hydrogen cyanide and benzoic acid.

(b) The usual hydrolytic agents used are (1) baryta water, (2) hydriodic acid, (3) concentrated hydrochloric acid, and (4) sulphuric acid (25 per cent). The last of these appears to be the best, as it produces less complex decomposition, e.g. less ammonia and more amino acids. The most marked feature of the products thus obtained is the predominance of amino acids.

A few simple proteins yield only two amino-derivatives; thus both **salmine** and **clupeine**, obtained respectively from the testicles of the salmon and herring, yield histidine. As a rule, the more complex proteins yield a considerable number of amino compounds, the number of such compounds and also their relative proportions varying with the protein.

## 1. AMINO ACIDS AND BASES FROM PROTEINS

1. **Mono-amino-mono-carboxylic Acids.**—Glycine = amino-acetic acid; Alanine =  $\alpha$ -amino-propionic acid; Valine =  $\alpha$ -amino- $\beta$ -methyl-*n*-butyric acid,  $(\text{CH}_3)_2\text{CH}\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}$ ; Leucine =  $\alpha$ -amino- $\gamma$ -methyl-*n*-valeric acid,  $\text{CHMe}_2\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ ; iso-Leucine =  $\alpha$ -amino- $\beta$ -methyl-*n*-valeric acid,  $\text{CH}_3\cdot\text{CH}_2\cdot\text{CHMe}\cdot\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ ; Norleucine =  $\alpha$ -amino-*n*-caproic acid; Phenylalanine =  $\alpha$ -amino- $\beta$ -phenyl-propionic acid,  $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ ; Tyrosine =  $\alpha$ -amino- $\beta$ -hydroxyphenylpropionic acid, *p*-OH $\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ ; Serine =  $\alpha$ -amino- $\beta$ -hydroxypropionic acid; Threonine =  $\alpha$ -amino-*p*-hydroxy-*n*-butyric acid with the configuration,



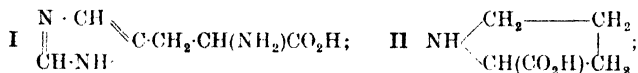
corresponding with that of *d*-threose; Cystine = di-( $\alpha$ -amino- $\beta$ -thiopropionic acid),  $\text{CO}_2\text{H}\cdot\text{CH}(\text{NH}_2)\cdot\text{CH}_2\cdot\text{S}\cdot\text{S}\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot$

$\text{CO}_2\text{H}$ ; Methionine =  $\alpha$ -amino- $\gamma$ -methylthiol- $n$ -butyric acid,  $\text{CH}_3\text{S}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}$ .

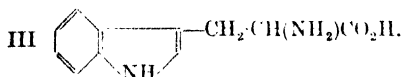
2. **Mono-amino-dicarboxylic Acids.**—Aspartic acid = amino-succinic acid; Glutamic acid =  $\alpha$ -amino-glutaric acid; Hydroxyglutamic acid =  $\alpha$ -amino- $\beta$ -hydroxyglutaric acid,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ .

3. **Diamino-mono-carboxylic Acids.**—Arginine =  $\alpha$ -amino- $\delta$ -guanidino- $n$ -valeric acid,  $\text{HN}=\text{C}(\text{NH}_2)\cdot\text{NH}(\text{CH}_2)_3\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}$ , which has been synthesized from ornithine (p. 251) and cyanamide (p. 313); Lysine =  $\alpha\epsilon$ -diaminocaproic acid.

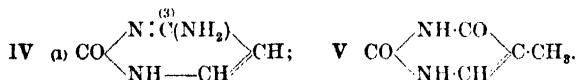
4. **Heterocyclic Amino-acids.**—Histidine =  $\alpha$ -amino- $\beta$ -iminazolepropionic acid (I); Proline =  $\alpha$ -pyrrolidene-carboxylic acid (II):



Hydroxyproline =  $\gamma$ -hydroxy- $\alpha$ -pyrrolidenecarboxylic acid; Tryptophane =  $\alpha$ -amino- $\beta$ -indolepropionic acid (III):



5. **Purine and Pyrimidine Bases.**—Guanine = 2-amino-6-oxypurine (p. 331); Adenine = 6-aminopurine; Cytosine = 3-amino-1-pyrimidone (IV) and thymine = 4-methyl-3-keto-2 : 3-dihydropyrimidone (V):



Most proteins also contain a carbohydrate radical, e.g. mannose, galactose, or frequently a hexosamine, i.e. they are glycosides.

Fischer's method of separating the amino-acids formed on hydrolysis of a protein was by fractionation of their methyl esters under very low pressures. A modified, and stated to be a more accurate, method is the fractionation of the esters of the acetylated acids. The percentages of the known amino-acids found in the four proteins, viz. gelatin, casein, gliadin and zein, varies from 90–103 per cent, indicating that there cannot be in the molecules of these proteins large quantities

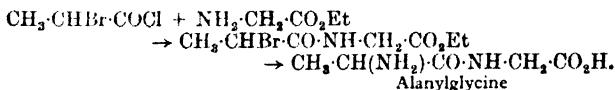


of hitherto unidentified acids, and glutamic acid is the chief constituent of the last three. These more accurate methods of estimation have rendered it possible to determine the molecular ratios of the different amino-acids in such proteins as gelatin, blood-fibrin and keratin (J. Biol. Chem., 1936, **115**, 77).

The carboxylic groups present in the hydrolytic products are probably not present in the original molecule, and it is highly probable that most of the amino-groups are not present as such, but are employed in uniting the various radicals together, since only some 10 per cent of the total nitrogen in albumin is eliminated as such on treatment with nitrous acid; in other words, the amino-group of one molecule reacts with the carboxylic group of another, yielding compounds with the group,  $\cdot\text{CO}\cdot\text{NH}\cdot$ , characteristic of acid amides. *Emil Fischer* and others have synthesized complex compounds of this type by the gradual condensation of amino-acids. Although none of the proteins has been so far synthesized, the products—the **polypeptides**—exhibit considerable analogy to the peptones.

The following general methods are used for the synthesis of polypeptides:

1. The chloride of a halogenated fatty acid is condensed with the ester of an amino-acid, the resulting ester hydrolysed, and the halogen then replaced by an amino-group by means of ammonia:

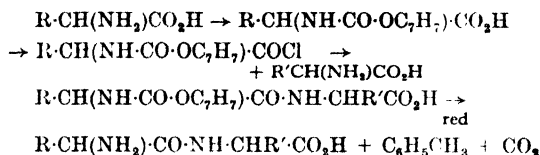


The dipeptide thus obtained can be converted into its acid chloride, and this condensed with a molecule of an ester of an amino-acid, e.g. glycine ester, yielding the compound  $\text{CH}_3\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{CO}_2\text{C}_2\text{H}_5$ , which on careful hydrolysis yields the corresponding acid—**alanyl-glycylglycine**—an example of a tripeptide. The operations can be repeated, and in this way compounds containing 18 amino-acid residues have been synthesized.

As the amino-acids obtained by hydrolysing natural proteins are optically active, *Fischer* used optically active acids and esters in his synthetical operations, the optically active acid being obtained by resolving its racemic benzoyl derivative by means of active bases and then removing the benzoyl group.

2. Another method consists in protecting the amino-group in an  $\alpha$ -amino-acid by converting into the *p*-toluene-sulphonyl derivative, forming the acid chloride, condensing with a second amino-acid, and finally removing the *p*-toluene-sulphonyl group with hydriodic acid and phosphonium iodide.

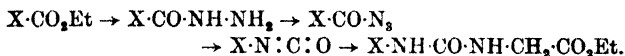
3. *Bergmann* and *Zervas* (B., 1932, 1192) protect the  $\text{NH}_2$  group by introducing the  $\cdot\text{CO}\cdot\text{O}\cdot\text{CH}_2\cdot\text{C}_6\text{H}_5$  group by the action of benzyl chloroformate, forming the acid chloride or azide and condensing with a second amino-acid, and finally reducing with hydrogen and palladium:



(cf. *Harrington* and *Bergmann*, Bio. J., 1935, 1602).

4. Glycylglycine can be obtained by heating ethylglycine when the anhydride, diketopiperazine,  $\text{NH} \begin{array}{c} \diagup \text{CO}\cdot\text{CH}_2 \\ \diagdown \text{CH}_2\cdot\text{CO} \end{array} \text{NH}$ , is formed, and hydrolysing this with dilute alkali.

5. Another method of obtaining polypeptides is through the azide (p. 213) of the acid. Thus starting with ethyl hippurate, this is converted into the hydrazide, and, finally, into the azide, which yields a carbimide when heated. The carbimide is condensed with the ester of an amino-acid, e.g. ethylglycine, yielding a product which can be transformed into an azide and the series of reactions repeated (*Curtius*, J. pr., 1916, 94, 85).



*Fischer* succeeded in synthesizing by his methods a polypeptide containing 18 amino-acid groups, viz. *l*-leucyl-triglycyl-*l*-leucyl-triglycyl-*l*-leucyl-octaglycyl-glycine with a molecular weight of 1213.

The position of the free amino-group in a complex polypeptide can be ascertained by the action of naphthalene- $\beta$ -sulphonyl-chloride, and hydrolysis with hydrochloric acid. Thus, alanyl-glycylglycine (a tripeptide) treated in this way gives naphthalene- $\beta$ -sulphonylalanine and glycine as hydro-

lytic products, indicating that the free amino-group is present in the alanyl residue. (B., 1916, 2449, 2838).

The optical rotation of an active polypeptide kept in contact with dilute alkali for a few days changes, and this has been shown to be due to the enolization of an inner—CHR·CO— group. In the case of a tripeptide the products of hydrolysis, viz. the inactive amino-acid isolated, will prove that this occupied the middle of the peptide chain.

A few polypeptides, e.g. tetrapeptides, have been isolated from the hydrolytic products of certain proteins.

The putrefaction of albumins gives rise not only to amino-acids, but also to aromatic and fatty acids (e.g. butyric acid, phenyl-acetic acid), indole, skatole, and cresol; further, to the basic **ptomaines** (the toxins produced in dead bodies), which include putrescine (from arginine) and cadaverine (from lysine), choline, muscarine, and neurine (p. 227). All of these are not poisonous, and many also occur in the vegetable kingdom. Only the amines derived from phenylalanine, tyrosine, tryptophan and histidine have marked physiological activity, and histamine derived from histidine is the most active.

## 2. CLASSIFICATION OF PROTEINS

**I. Simple Proteins** yielding amino-acids or derivatives on hydrolysis.

(a) *Albumins*.—Soluble in pure water and coagulated by heat. Egg-albumin, serum albumin, leucosin (wheat), legumin (peas).

(b) *Globulins*.—Insoluble in water but soluble in neutral salt solutions. Muscle globulin, edestin (wheat), phaseolin (beans), tuberin (potato), arachin (ground nut).

(c) *Gluteins*.—Insoluble in neutral solvents but soluble in acids and alkalis. Glutenin of wheat.

(d) *Prolamins*.—Soluble in 70–80 per cent alcohol, but insoluble in water, absolute alcohol or neutral solvents. Gliadin (wheat), zein (maize), hordenin (barley).

(e) *Scleroproteins* or Albuminoids.—The proteins present in the skeletal structure of animals and in skin, hair, &c. Collagen which boiled with water gives gelatin. Elastin from ligaments and keratin from hoofs.

(f) *Histones*.—Soluble in water and fairly concentrated ammonia and ammonium salts, but insoluble in dilute am-

monia. Coagulated by heating, but coagulum soluble in very dilute acid. Globin from hæmoglobin.

(g) *Protamines*.—The simplest proteins. Soluble in water. Not coagulated by heat. Strongly basic and on hydrolysis yield only 2 or 3 amino-acids. Salmine and sturine from fish testicles.

**II. Conjugated Proteins.**—Protein combined with another molecule in a form other than salt.

(a) *Nucleoproteins*.—Compounds of a protein with a nucleic acid, e.g. wheat germ contains triticonucleic acid, and the thymo-gland a compound of protein with thymonucleic acid.

(b) *Glycoproteins*.—Compounds of proteins with carbohydrates, e.g. mucins: slimy proteins with a lubricating function secreted by salivary glands and mucous cells of alimentary canal, secretion of slugs, &c., on hydrolysis usually give an aminohexose.

(c) *Phosphoproteins*.—Proteins with phosphorus in some form other than a nucleic acid or lecithin. Caseinogen (milk), ovovitellin (egg-yolk).

(d) *Chromoproteins* or *Hæmoproteins*.—Protein combined with hæmatin or analogous compound. Hæmoglobin and hæmocyanin, proteins with respiratory functions found in blood of all vetebrates.

(e) *Lecithoprotein*.—Compounds of protein and lecithin.

### III. Derived Proteins.

1. **Primary protein derivatives** formed by gentle hydrolytic changes in proteins.

(a) *Proteans* formed by action of water, very dilute acids, or enzymes on proteins. Casein from curdled milk, fibrin from coagulated blood.

(b) *Metaproteins* formed by further action of acid on protein. Soluble in very weak acids or alkalis, but insoluble in neutral solvents. Acid and alkali albumins or albuminates.

(c) *Coagulated proteins* formed by action of heat or alcohol on protein solutions. Precipitated egg albumin.

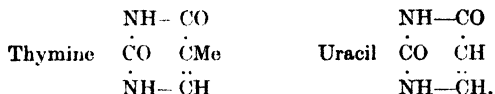
2. **Secondary protein derivatives** obtained by further hydrolysis of protein molecule.

(a) *Proteoses*.—Soluble in water, not coagulated by heat, and precipitated by salting out their solutions with ammonium sulphate. "Peptones" consist largely of proteoses.

(b) *Peptones proper*.—Soluble in water, not coagulated by heat, and not precipitated from their solutions by ammonium



are that the animal acid gives *d*-2-deoxyribose,  $\text{HO}\cdot\text{CH}_2[\text{CH}\cdot\text{OH}]_3\cdot\text{CH}_2\cdot\text{CHO}$ , with the bases guanine, adenine, cytosine, and thymine, whereas the plant acid yields *d*-ribose, guanine, adenine, cytosine, and uracil:



It is suggested that each molecule of phosphoric acid forms an ester with the sugar, and that the cyclic bases are united to the four sugar residues in the order guanine, cytosine, uracil (or thymine), and adenine.

The hæmoglobin, the colouring matter of the red corpuscles of mammalian blood, is a compound of hæmatin (Chap. LXIV, D1) with a globulin and has a mol.-weight of roughly 68,000. The clotting of blood is due to the presence of fibrinogen.

For the amino-acids and bases derived from different proteins and their relative amounts, cf. *Lloyd and Shore*, 2nd Edition, p. 136.

### 3. STRUCTURE OF PROTEINS

In a fairly complex polypeptide or protein molecule the amino-acids appear to be arranged in a fixed order, as shown by the pattern of X-ray photos. *Bergmann and Zervas* (J. biol., 1936, **113**, 34) by the careful hydrolysis of clupein (a protamine) from herring roe found that with the enzyme protaminase the protein gives 2 mols. of clupean (a polypeptide) and 4 mols. of arginine, and that clupean with trypsin and other enzymes yields 2 mols. of a dipeptide and 3 of a tripeptide. Each molecule of dipeptide on hydrolysis gave arginine and an amino-acid, and each molecule of tripeptide 2 mols. of arginine and one of amino-acid, and they suggest that the only arrangement in harmony with these results is:



A = arginine residue.

M = mono-amino-acid residue.

———— = fission produced by trypsin.

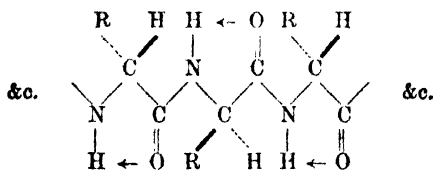
----- = fission produced by protaminase.

*Bergmann* and his co-workers have developed this idea and have worked out the ratios in which the different residues occur in ox-fibrin, egg-albumin, &c. They calculate from the results of careful analysis of hydrolytic products the number of gram-mols. of each amino-acid formed from 100 gm. of protein, and from these data calculate the frequency of the occurrence of each amino-acid. For egg-albumin the frequencies are glutamic acid 1 in 8, aspartic acid 1 in 18, methionine, lysine and arginine each 1 in 24, tyrosine 1 in 36, and histidine and cysteine each 1 in 72. The smallest number of residues which can give these frequencies is 288, and hence the molecule of egg-albumin must contain 288 or some multiple of 288 residues, i.e. a mol.-weight of 35,700 or some multiple of this. The minimum value agrees roughly with that determined by the ultra-centrifugal method.

All the amino-acids forming the residues in a protein molecule have the same spatial configuration, i.e. in compounds of the type



the relative positions of the 4 groups are always the same, quite independent of the nature of R. They all belong to the *l* series (for absolute configuration, cf. *Rainey*, *Nature*, 1937, 140, 150).



The molecule has a zigzag structure with the R groups alternatively above and below the  $\text{C}\cdot\text{NH}\cdot\text{CO}\cdot\text{C}$  plane. The unit  $\text{N}\diagdown\text{C}\diagup\text{C}$  is repeated and its length is 3.5 Å. The co-ordinate links (H bridges) result in chelate rings.

In silk fibroin built up of alternate glycine and alanine residues it follows that all the  $\text{CH}_3$  groups lie in the same plane, as they occur alternatively with H.

## B. Protein Foodstuffs

The changes which protein foodstuffs undergo in the animal system have been the subject of much study (*Hopkins*, J. C. S., 1916, 629; cf. also C. and I., 1933, 173). It is generally agreed that the proteins are ultimately hydrolysed in the intestine to their ultimate constituents, the amino- or imino-acids, and that these acids are absorbed by the blood and carried to the different tissues, where they can undergo (1) synthesis to protein compounds required for growth and replacement of that lost by wear, e.g. skin, secretions of glands, milk, mucus, &c.; (2) oxidation, when present in abundance, to supply part of the heat required by the organism; and (3) conversion to purine derivatives, adenine and guanine, and the excretory substances, allantoin and uric acid. This conclusion is largely based on the following facts: (a) completely hydrolysed proteins, e.g. casein, are as effective as nutrients as the unhydrolysed proteins; (b) in the blood the bulk of the organic nitrogen is present as amino-acids and not as complex polypeptides or proteins (this has been proved by *van Slyke* by measurements of nitrogen evolved by the action of nitrous acid on the blood); (c) when food proteins are introduced intact into the blood, reactions follow which are quite different from those which follow the normal ingestion of food.

Proteins of animal origin are digested more readily than those of vegetable with the exception of uncooked white of egg. This may be due to the fact that vegetable proteins are protected from enzyme action by non-digestible cellulose. The protein of meat if not over-cooked is the most readily digested. In many cases digestibility is increased by cooking but is largely impaired by over-cooking.

As the result of careful experiments it has been proved that the following amino-acids and bases must be supplied in the food as they cannot be formed in the animal system itself.

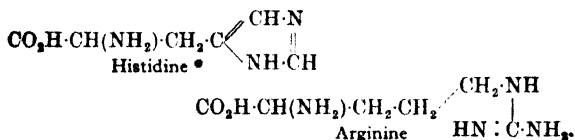
(1) Tryptophan (*d*, *l*, or *dl* equally good). (2) Lysine. (3) Histidine (*l* more effective than *d*). It is probably required for the production of the purine bases of nucleic acid and for the formation of histamine. (4) Arginine. (5) Methionine,  $\gamma$ -methylthiol- $\alpha$ -amino-*n*-butyric acid,  $\text{CH}_3\text{S}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}$ , required as source of S for organic sulphur compounds. It can be replaced by cystine. (6) Phenylalanine. It cannot



be replaced by tryosine, but is probably the precursor of this and of thyroxin and adrenaline. (7) Leucine and *iso*-leucine.

On the other hand, serine, glutamic acid, hydroxyglutamic acid, proline, and oxyproline need not be present in the food, and can presumably be synthesized in the body at rates necessary to meet the requirements of natural growth.

It is thus clear that the animal system is incapable of synthesizing the indole group (tryptophan), or the guanidine (arginine), or iminazole (histidine) groups, and it is essential that the food supplied should contain such groups. If arginine is supplied, the system appears to be capable of converting this into histidine; the close relationship between the two compounds is illustrated in the two formulæ:



## LXVIII. VITAMINS AND HORMONES

Compounds physiologically of vital importance in animal metabolism are those belonging to the two groups the *Vitamins* and the *Hormones*, both of which are characterized by the fact that minute amounts play such an important biochemical rôle. The vitamins are not formed in the body but are introduced in the food utilized by the animal, whereas the hormones are formed in the body, usually in special glands.

\* For synthesis, see *Pyman*, J. C. S., 1916, 186; and for synthesis of *Carnosine*,  $\beta$ -alanylhistidine,



cf. also *Barger* and *Tutin*, Bio. J., 1918, 402; it occurs in *Liebig's extract* of beef.

## A. Vitamins \*

This name was introduced by *Funk* to comprise certain accessory factors in normal dietary,† and from 1912 our knowledge of the number, structure, and physiological importance of these compounds has increased at a rapid rate. They are usually divided into the two groups I, Fat soluble, and II, Water soluble. To group I belong the compounds A, D, D<sub>2</sub>, D<sub>3</sub>, and to group II the compounds B<sub>1</sub>, B<sub>2</sub>, C, E. The absence of any one in the dietary causes some definite disease or a lapse of certain physiological activities.

From a chemical standpoint, the different vitamins are not closely related but belong to very different groups of compounds. Their structures have been determined in many cases and several have been synthesized in the laboratory, and many of these have been discussed in the chapters dealing with the groups of compounds to which they belong. Some ten distinct vitamins are now recognized.

**Vitamin A, Axerophthol**, is associated with animal fats and is present in relatively large quantities in the livers of fishes. In its absence young animals fail to grow, degenerative changes in the epithelial cells which form the outer layer of the body take place, and a pathological condition of the eyes known as xerophthalmia is set up. An adequate supply protects against certain types of infection. The addition of cod-liver or better halibut-liver oil to the dietary gives the necessary vitamin. Its structure is closely related to that of the yellow colouring matters of the carotenes (Chap. LXIV, A1), and can be formed in the animal system from the carotenes contained in green vegetables and carrots.

A second constituent, A<sub>2</sub>, appears to be present in some oils, and in freshwater fish largely replaces A. It may be vitamin A with an additional  $\cdot\text{CH}:\text{CH}$  before the  $\cdot\text{CH}_2\cdot\text{OH}$  group, and thus have 6 conjugated olefine links.

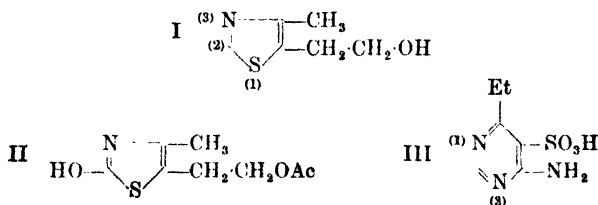
**Vitamin B<sub>1</sub>, Aneurin.†** A deficiency of this leads to the

\* *F. G. Hopkins, Nature, 1935, 135, 708; Karrer, Chem. Rev., 1934, 7; Vitamins in Theory and Practice, 3rd Edition, L. J. Harris, Cambridge, 1938.*

† The term advitant has been suggested by *Armstrong*.

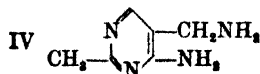
‡ In America sometimes termed Vitamin F. For details, see Vitamin B<sub>1</sub> and Beri-beri, *L. J. Harris, London, 1938; also Williams, Sci., 1938, 87, 559.*

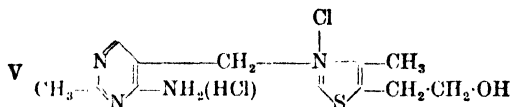
disease "beri-beri". Its presence appears to be essential for the normal process of carbohydrate metabolism and for the maintenance of a normal equilibrium in the nervous tissues. It is present in the cortical parts of grains, e.g. husk of rice, and the use of polished rice in tropical countries leads to the occurrence of beri-beri. It also occurs in yeast together with B<sub>2</sub>, and the relative proportions of the two vary considerably with different species. It is the only vitamin containing sulphur, and its hydrochloride has the composition  $C_{12}H_{18}ON_4SCL_2$ , and by the action of acid bisulphite solutions *Williams* (J. A. C. S., 1935, 229) obtained quantitative yields of the two products: (a) a sulphonic acid  $C_6H_9O_3N_3S$ , and (b) a base  $C_6H_9ONS$ . The latter compound when oxidized gives the known 4-methylthiazole-5-carboxylic acid and therefore has structure I, and this has been confirmed by synthesis



(*Andersag and Westphal*, 1937) in the following manner:  $\gamma$ -Acetopropyl acetate,  $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OAc$ , brominated gives  $CH_3 \cdot CO \cdot CHBr \cdot CH_2 \cdot CH_2 \cdot OAc$ , and this with barium thiocyanate gives  $CH_3 \cdot CO \cdot CH(S \cdot C : N) \cdot CH_2 \cdot CH_2 \cdot OAc$ , which readily isomerizes in acid solution to 2-hydroxy-4-methyl-5-acetoethyl-thiazole II, and by replacing the OH by Cl with the aid of  $POCl_3$ , and the removal of Cl by zinc dust and acetic acid, the acetyl derivative of I is formed.

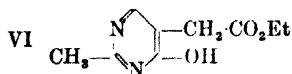
The acid component (a) was regarded by *Williams* as 6-ethyl-4-amino-pyrimidine-5-sulphonic acid, but *Andersag and Westphal* (B., 1937, 2035) have proved that one of the products obtained by oxidizing aneurin with acid permanganate is identical with 2-methyl-4-amino-5-amino-methyl-pyrimidine IV. The acid is the corresponding 6-sulphonic acid





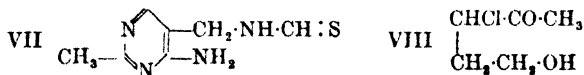
and hence aneurin is to be represented by V.

The stages in the synthesis of IV are: (1) ethyl formylsuccinate condenses with acetamidine hydrochloride in the presence of sodium ethoxide, yielding ethyl (2-methyl-4-hydroxypyrimidyl)-5-acetate VI. (2) Replacement of OH by Cl and then by  $\text{NH}_2$  by the action of liquid ammonia under pressure, when the ester is also converted into the acid amide. (3) The conversion of the amide  $\text{---CH}_2\text{---CO---NH}_2$  into the amine  $\text{---CH}_2\text{---NH}_2$  by the *Hofmann* reaction.



The vitamin has been synthesized by three methods, viz. *Williams* and *Clive* (J. A. C. S., 1936, 1504; 1937, 1052), *Todd* and *Bergel* (J. C. S., 1937, 364), and *Andersag* and *Westphal* (B., 1937, 2049).

The second synthesis consists in condensing 4-amino-2-methyl-5-thioformamidopyrimidine VII with methyl  $\alpha$ -chloro- $\gamma$ -hydroxypropyl ketone VIII,



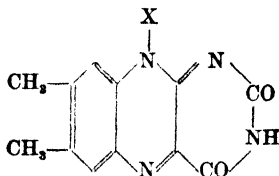
and the third method consists in converting the diamine IV into the corresponding alcohol  $\text{---CH}_2\text{---NH}_2$  into  $\text{---CH}_2\text{---OH}$  by nitrous acid, then by the action of an acetic acid solution of HBr converting  $\text{---CH}_2\text{---OH}$  into  $\text{---CH}_2\text{Br}$ , and the final condensation of this 2-methyl-4-amino-5-bromomethyl-pyrimidine in the form of its hydrochloride with 4-methyl-5-hydroxyethyl-thiazole (I).

B1 plays a part in oxidations in the brain.  $\alpha$ -Hydroxypyridine and 2:6-dihydroxyquinoline have physiological properties similar to those of B1 but far less pronounced.

**Vitamin B2** (or in America G) is also present in yeast, but is more stable to heat than B1. Its absence in a dietary produces serious skin lesions in animals similar to those met

with in the human disease—pellagra—producing dermatitis of the face and hands.

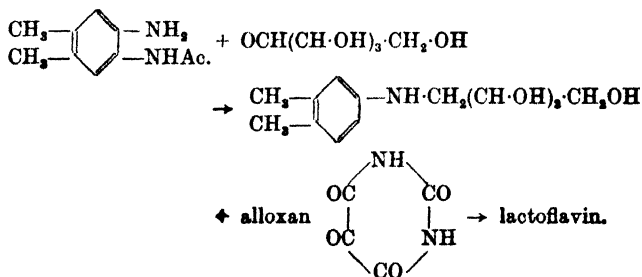
It is soluble in water, occurs in yeast, milk, lean meat, and green vegetables. At one time it was regarded as identical with lactoflavin, 6 : 7-dimethyl-9-*d*-riboflavin phosphate,



where  $X = \cdot CH_2(CH \cdot OH)_3 \cdot CH_2OH$ , with a phosphoric acid group in position 5', but as this compound does not prevent "rat-pellagra" the two cannot be identical, and it is possible that B2 is a mixture of lactoflavin with other compounds.

Nicotinic acid (Chap. XLIII, B.) appears to be one of these, and is a specific against pellagra. Another is vitamin B6, which prevents rat dermatitis. This has been termed **adermin**, and has the composition  $C_8H_{12}O_3NCl$ ; and a third is the compound which prevents dermatitis in chickens.

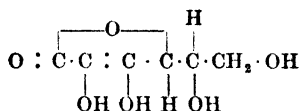
Lactoflavin is a vitamin which promotes growth and has been synthesized in the following manner:



Numerous flavins isomeric and stereoisomeric with lactoflavin but containing different carbohydrate groups have been synthesized, but the only one with physiological activity is the ribo one.

**Vitamin C, Ascorbic Acid**, is the antiscorbutic vitamin present in most fresh foods, especially fruits and green vegetables, but varies in amount from species to species and is not

present in cereals. Freshly picked parsley, broccoli and kale contain three times as much as citrus fruits. It is less stable than most of the other vitamins, and is destroyed when foods are kept for a long time, dried or heated. It is extremely sensitive to oxidation and reduction, and one of its functions is to convey oxygen to the tissues as it is needed. It is probably formed in the body and stored in the suprarenal gland. The daily requirement is 40–80 mg., and lack of it produces scurvy. It was first isolated from the adrenal gland, then from cabbage, afterwards from oranges, and finally from big red capsicum (1932), when as much as 1 lb. was prepared. In the crude form it is extremely difficult to handle, especially in presence of glutathione (p. 1216), but is more stable when pure. Its structure as 3-keto-*l*-gulonolactone has been proved by its reactions and by its synthesis (cf. Chap. LVI, E.). It was the first vitamin to be synthesized.



**Vitamin D\*** is the antirachitic vitamin, and usually accompanies A in animal fats, particularly fish-liver oils. The percentage of the two is high in mackerel, tunny, and sea bass (order *Percomorphi*) and rock fish and sculpin (order *Cataphracti*). The *Heterosomata*, e.g. halibut and flat fish, are richest in A, but *Holconoti*, e.g. viviparous perches, in D. About 75 per cent of the liver oils are more potent in D than cod-liver oil, and nearly all are richer in A. Some percomorph oils are 100–400 times more potent than cod-liver oil, and some of these, e.g. halibut-liver oil, are supplanting it in medicine. It is also present in the fermented shell of cacao, which is thus a valuable feeding stuff for cows, as the vitamin passes into the milk.

Vitamin D has not been obtained in a pure state, only in the form of a viscous oil, and hence no characteristic physical data are known. For several years it was thought to be identical with calciferol, i.e. D<sub>2</sub>, the synthetic vitamin obtained by ultra-violet irradiation of ergosterol (for structure, cf. Chap. LXII, C.), but several important differences have been pointed

\* *Vitamin D*. C. J. Reed and others, London, 1939.



of the  $\alpha$ -compound and 0.75 of the  $\beta$ . Compare Report on Vitamin E, Soc. Chem. Ind., 1939.

**Vitamin K<sub>1</sub>** (1934) is a thermo-stable, fat soluble substance present in hog's-liver fat and in green vegetables, e.g. alfa-alfa, and a deficiency of this vitamin produces hæmorrhage, anæmia, and a prolonged blood clotting time in chickens. It is 2-methyl-3-phytyl-1:4-naphthaquinone (*Fieser*, 1939, cf. C. and I., 1940, 233).

Several vitamin preparations are now manufactured and added to food stuffs, e.g. margarine, bread, milk, glucose, &c. It is to be noted that excess of vitamins A and D is harmful, D causing the deposition of calcium phosphate in different parts of the body (*Drummond*, C. and I., 1935, 744).

For details of certain vitamins, cf. *Edyvean*, C. and I., 1938, 1155.

## B. Hormones \*

Most of the hormones are chemical compounds formed in particular ductless glands and do not pass directly into the alimentary canal but into the blood system. They are mostly hydrolysed in the canal, and therefore should not be administered *per os* but hypodermically. Recently hormones of vegetable origin have been isolated; they are termed **auxines** and are essential for the development of higher plant life.

A few of the vitamins appear to be capable of synthesis in the tissues of certain species and hence approach the hormones.

The number of hormones is considerable, and the following list includes the most important:

1. **Acetylcholine**,  $\text{OAc}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NMe}_3\cdot\text{OH}$ , formed in the spleen and body tissues. It is produced as required and is not stored. Stimulation of the parasympathetic nerves liberates this compound at nerve endings and maintains the tone of the muscles.

2. **Histamine**,  $\text{C}_6\text{H}_9\text{O}_2\text{N}_3$ , formed in the lungs and body tissues. Not stored.

3. **Adrenaline**,  $\text{C}_9\text{H}_9\text{O}_3\text{N}$ , stored in the adrenal gland.

4. **Thyroxine**,  $\text{C}_{15}\text{H}_{11}\text{O}_4\text{NI}_4$ , stored in the thyroid gland.

5. **Insulin**, stored in the pancreas.

6. **Parathormone**, stored in the parathyroid gland.

7. **Secretin**, stored in the duodenum.

\* F. Wokes, *Applied Biochemistry*, Chap. XI, 1937.



8a. **Oxytocin**, and 8b. **Vasopressin**, stored in the pituitary gland.

- |   |                        |
|---|------------------------|
| 9. <b>Oestrone</b> , $C_{18}H_{22}O_2$ .                    | } Female sex hormones. |
| 10. <b>Progesterone</b> , $C_{21}H_{30}O_2$ .               |                        |
| 11. <b>Androsterone</b> , $C_{19}H_{30}O_2$ .               | } Male sex hormones.   |
| 12. <b>Testosterone</b> , $C_{19}H_{28}O_2$ .               |                        |
| 13. <b>Corticosterone</b> , produced by the adrenal cortex. |                        |

Even minute quantities of hormones have detectable effects varying from a dilution of 1 in  $6 \times 10^6$  for secretin to 1 in  $6000 \times 10^6$  for acetylcholine.

1. **Acetylcholine**,  $OAc \cdot CH_2 \cdot CH_2 \cdot NMe_3OH$ , has been isolated from the spleen of the ox and horse (1929), and has also been obtained from plant tissues.

2. **Histamine**, 2-(4-iminoazoly)-ethylamine or 4-( $\omega$ -amino-NH-CH ethyl)-glyoxaline,  $\begin{array}{c} \text{NH-CH} \\ | \\ \text{CH} \end{array} \begin{array}{l} \diagup \\ \diagdown \end{array} \begin{array}{l} \text{C-CH}_2 \cdot \text{CH}_2 \cdot \text{NH}_2 \\ \text{CH=N} \end{array}$  is probably formed by the decarboxylation of histidine (Chap. LXVII, A1) and has been synthesized.

3. **Adrenaline**. This hormone is formed in the suprarenal gland, increases the blood pressure, liberates glycogen from the liver, and increases all emotions due to vascular and visceral reactions. It arrests hæmorrhage from capillaries or small veins, localizes the action of anæsthetics, eases asthmatic attacks, and restores action of heart after surgical operations. Its structure as the 3:4-dihydroxy derivative  $(OH)_2C_6H_3 \cdot CH(OH) \cdot CH_2 \cdot NHMe$  has been proved by synthesis (Chap. LXV, D.).

4. ***l*-Thyroxine** occurs in the secretion of the thyroid in the form of the peptide compound thyreoglobulin, from which it can be obtained by the action of enzymes. It is responsible for the primary oxidative changes in the body, and about 1 mg. per day is necessary. If there is an excess oxidation is too rapid, life burns too fast, weight is lost, the heart beats quicker, and restless activity and nervous irritability ensue. If the secretion is on the low side, life slows down, fat accumulates, and the mental processes are dulled. If deficiency occurs in early childhood, mentally deficient dwarfs result unless thyroid gland extract is administered in time.

The structure as the 3:5:3':5'-tetraiodo-4-hydroxy-phenyl ether of tyrosine (Chap. XXVI, A3)  $OH \cdot C_6H_2I_4 \cdot O \cdot$

$\text{C}_6\text{H}_5\text{I}_2\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}$ , has been established by synthesis (Harrington, Bio. J., 1926, 300; J. S. C. I., 1926, 931). The stages are  $p\text{-MeO}\cdot\text{C}_6\text{H}_4\text{Br} + \text{HO}\cdot\text{C}_6\text{H}_5 \rightarrow \text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{C}_6\text{H}_5$ . *Tiemann-Reimer* reaction  $\rightarrow \text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot$

$\text{C}_6\text{H}_4\cdot\text{CHO} \rightarrow$  with  $\text{CH}_2\begin{matrix} \text{CO}\cdot\text{NH} \\ | \\ \text{NH}\cdot\text{CO} \end{matrix}$  gives  $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot$   
 $\text{CH}:\text{C}\begin{matrix} \text{CO}\cdot\text{NH} \\ | \\ \text{NH}\cdot\text{CO} \end{matrix}$ , and this on hydrolysis gives (II) the *p*-hydroxy-

phenyl ether of tyrosine  $\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}$  (II), which with iodine yields thyroxine. Another synthesis consists in condensing quinol monomethyl ether with 3 : 4 : 5-triiodonitrobenzene to 2 : 6-diiodo-4'-nitro-4'-methoxy-diphenyl ether  $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{C}_6\text{H}_2\text{I}_2\text{NO}_2$ . This can be transformed into the amine, then the nitrile, and finally into the aldehyde,  $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{C}_6\text{H}_2\text{I}_2\cdot\text{CHO}$ , which condenses with hippuric acid,

giving the azlactone  $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{C}_6\text{H}_2\text{I}_2\cdot\text{CH}:\text{C}\begin{matrix} \text{CO}\cdot\text{O} \\ | \\ \text{N}\equiv\text{CPh} \end{matrix}$  from

which on hydrolysis the benzamino-cinnamic acid  $\text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{C}_6\text{H}_2\text{I}_2\cdot\text{CH}:\text{C}(\text{NHCOPh})\text{CO}_2\text{H}$  is formed. This with hydriodic acid and phosphorus yields  $\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{C}_6\text{H}_2\text{I}_2\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}$ , from which thyroxine can be obtained by treatment with iodine in ammoniacal solution. The *dl*-compound has been resolved by means of *l*- $\alpha$ -phenylethylamine.

The iodine required for its formation in the body is extracted from the blood, which obtains it from the food supply.

Certain diseases due to lack of thyreoglobulin can be rectified by the addition of minute quantities of iodine to the food or water supply, or even added to fertilizers of the soil in which the crops are grown.

5. **Insulin** occurs in the internal secretion which the pancreas discharges into the blood system and varies with the concentration of sugar present in the blood. Its functions appear to be to remove all blood sugar in excess of 0.10 per cent, to convert it into glycogen which is stored in the liver or muscular tissues. If the discharge from the pancreas is deficient, glucose accumulates in the blood and tissues and the kidneys are no longer able to prevent its passing into the urine. Diabetes results and is accompanied by emaciation and general debility. At later stages fat metabolism is disturbed and hydroxybutyric and aceto-acetic acid pass into

the urine. The remedy is subcutaneous injection of insulin extracts obtained from the pancreas of the ox, pig or sheep. The method of isolation is difficult on account of its sensitiveness to proteolytic enzymes present. The method used is largely due to *Harrington*.

Its structure is that of a protein, and its hydrolytic products are cystine, tyrosine, glutamic acid, leucine, arginine, histidine and lysine. It is readily methylated and the product readily demethylated by 0.1N, NaOH at 0°. Its probable composition is  $C_{45}H_{69}O_{14}N_{11}S, 3H_2O$ .

An excess of insulin acts as a poison and careful administration is necessary. The antidote is glucose.

6. **Parathormone** is also a protein type of compound and controls the calcium content of the blood.

7 and 8 are two active principles from the posterior pituitary gland. The first stimulates the contraction of the uterine muscles and the second has a diuretic effect. Little is known of their composition.

9-12. **Sex hormones** (*Ruzicka*, Chem. Rev., 1937, 69). The investigation of these dates from 1929, and it is remarkable that, although they have been isolated in small amounts only, their properties, structures, and relationships should have been worked out and their syntheses completed within six years, largely due to the work of *Butenandt* and his co-workers. The female and male hormones appear to be formed respectively in the ovaries and testes under the stimulation of secretions (gonodotropic hormones) from the anterior lobe of the pituitary, and these are the primary factors in sexual development, and the removal of the anterior lobe inhibits sexual development and produces atrophy of the sexual organs. Little is known of these primary hormones, but the secondary male and female hormones have all been shown to contain the cholane skeleton (for details, cf. Chap. LXII, D.).

**Oestrone**,  $C_{18}H_{22}O_2$ , the follicular hormone (1929), occurs in pregnancy urine (e.g. 1 mg. per litre). It develops the genital organs of the female, e.g. uterus and vagina, and produces the secondary female characteristics, e.g. mammary glands, and also possesses other functions. It also occurs in the urine of the stallion (17 mg. per litre), and is met with to a limited extent in the vegetable kingdom, e.g. palm kernel extract and female willow flowers.

Other compounds with similar properties and found accom-

panying oestrone are **oestradiol**,  $C_{18}H_{24}O_2$ ; **oestriol**,  $C_{18}H_{24}O_3$ ; **equilin**,  $C_{18}H_{20}O_2$ , and **equilenin**,  $C_{18}H_{18}O_2$ .

**Progesterone** (1934) crystallizes in prisms, m.-pt.  $128^\circ$ , or needles, m.-pt.  $121^\circ$ , and has  $[\alpha]_D + 192^\circ$ , and forms a dioxime, m.pt.  $243^\circ$ . It is termed the corpus luteum hormone, and unlike oestrone is largely specific in its physiological activity; no naturally occurring compounds, even the closely related diol, pregnandiol (both CO reduced to  $CH\cdot OH$  and no double bond), accompanying it is physiologically inactive. The compound 17-methyltestosterone has an activity about one-sixth of that of progesterone.

The male hormone **androsterone** has m.-pt.  $182^\circ$ – $183^\circ$  and  $[\alpha]_D + 94.5$  and forms an acetate, oxime, and semicarbazone, and on complete reduction by *Clemmensen's* method yields the saturated hydrocarbon **androstane**, m.-pt.  $49^\circ$ – $50^\circ$ . It is accompanied by **dehydro-iso-androsterone**,  $C_{19}H_{28}O_2$ , which is less active than androsterone but possesses oestrogenic activity, and on reduction yields a secondary alcohol which is three times as active as the ketone. **Androstandione** is isomeric with the above and **testosterone**, also  $C_{19}H_{28}O_2$  (10 kilos testes yield 1 mg.), has m.-pt.  $154^\circ$ ,  $[\alpha]_D + 109^\circ$ , and yields an acetate, benzoate, and oxime with characteristic melting-points, and has the absorption spectrum of an  $\alpha\beta$ -unsaturated ketone.

All the four male hormones produce the same qualitative physiological actions but with marked quantitative differences, testosterone being the one with the best-defined properties. They all affect the genital tracts and are of importance in the formation of the external characteristics of the male, e.g. formation of horns in the stag and of the comb of the cock.

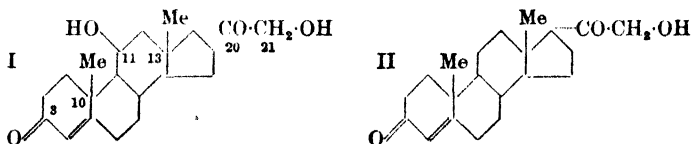
Testosterone displays its maximum biological activity when esterified, more particularly the propionate ( $O\cdot CO\cdot CH_2\cdot CH_2\cdot CH_3$  in position 17; formula, Chap. LXII, D.). This is slowly hydrolysed, yielding the hormone which is rendered more readily absorbable by the propionic acid also formed. The 17-methyl ether is also more active than the hydroxyl compound.

The terms male and female hormones are largely relative, as a given hormone affects both male and female organs, but one more than the other, and in most cases a given hormone can be obtained from both males and females.

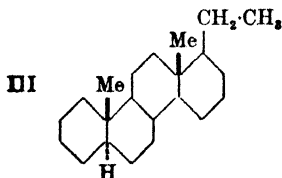
**Androstenediol** combines in a marked degree the physiological properties of both male and female hormones.

The hormones are probably not present in the free state in urine, &c., but combined with glycuronic acid (Bio. J., 1936, 57, 2250).

13. **Cortin**, the hormone of the adrenal cortex, regulates and maintains normal quantities of fluid in the vascular system. In its absence the normal blood pressure falls and a thickening of the blood occurs, due to passage of fluid through the walls of the vessel. An increase in red blood corpuscles occurs, also an increase in the frequency of heart beats accompanied by a diminution in the action of the kidneys. A crystalline compound, **corticosterone** (I),  $\Delta^4$ -pregnene-11 : 21-diol-3 : 20-dione, which is closely related to hydroxyprogesterone (II), has been isolated. Compound II also shows certain cortical activity.



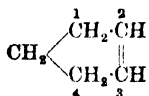
Careful examination of the adrenal cortex has shown the presence of at least 24 different steroids closely allied to pregnane or *allopregnane* (allo-10 : 13-dimethyl-17-ethylcyclopentenophenanthrene (III)). For summary, see Rep., 1938, 293.



The anterior and posterior lobes (A. L. P. and P. L. P.) of the pituitary contain numerous hormones. The former contains growth hormones, the primary sex hormones (gonodotropic hormones), and thyretropic hormones. The hormones of the latter (a) raise blood pressure, (b) stimulate contraction of the uterus, (c) check diuresis, (d) aid secretion of milk, and (e) increase intestinal peristaltic activity.

### C. Plant Hormones or Auxins \*

The bending of plant shoots towards light is due to the formation of a plant hormone (*Kögl*, B., 1935, 16) which is known in two forms, A and B. Both are regarded as derivatives of  $\Delta^2$ -cyclopentene. A has  $\cdot\text{CHMeEt}$  substituents in



positions 1 and 4 and the long chain  $\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$  in 2, and B has the same groups in 1 and 4 but  $\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  in 2.

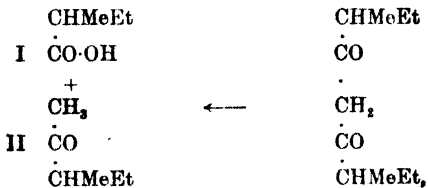
The structure of A is based on the following facts:

1. When oxidized with permanganate it yields an optically active dibasic acid, in all probability a dibasic acid of the type  $\text{CO}_2\text{H}\cdot\text{CHR}\cdot\text{CH}_2\cdot\text{CHR}'\cdot\text{CO}_2\text{H}$ , i.e. a substituted glutaric acid, as it yields an anhydride and not a ketone on heating, and hence the original ring was a 5 C and not a 6 C ring (cf. p. 1109). It is readily brominated by the *Hell-Valhard-Zelinsky* method, yielding an  $\alpha\alpha'$ -dibromo acid, and from this the corresponding dihydroxy acid is formed by the action of moist silver oxide,  $\text{CO}_2\text{H}\cdot\text{CR}(\text{OH})\cdot\text{CH}_2\cdot\text{CR}'(\text{OH})\cdot\text{CO}_2\text{H}$ .

2. The methyl ester of this acid with magnesium methyl iodide yields the ditertiary glycol,  $\text{OH}\cdot\text{CMe}_2\cdot\text{CR}(\text{OH})\cdot\text{CH}_2\cdot\text{CR}'(\text{OH})\cdot\text{CMe}_2\cdot\text{OH}$ .

3. On oxidation with lead tetracetate the terminal  $\cdot\text{CMe}_2\cdot\text{OH}$  groups are split off as acetone and the diketone  $\text{R}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{R}'$  is formed.

4. On hydrolysis the diketone gives *only d-a-methyl-butyr*ic acid (I) and methyl sec-butyl ketone (II),



\* *Kögl*, C. and I., 1938, 49.

at once indicating the symmetrical structure of the diketone.

5. The symmetrical structure of auxin A follows from this,

viz. a  $\text{CH}_2$   $\begin{array}{c} \diagup \text{C}(\text{CHMeEt})\cdot\text{C} \\ \diagdown \text{C}(\text{CHMeEt})\cdot\text{C} \end{array}$   $\parallel$  structure, and the nature of the

side chain in 2 follows from the fact that it contains a  $\text{CO}_2\text{H}$  and 3 OH groups and does not readily yield a lactone, and hence has no OH group on the  $\gamma$ -position.

Urine also contains a hormone *heteroauxin* which stimulates plant growth, and this has been proved to be indolyl-3-acetic

acid,  $\text{C}_8\text{H}_7$   $\begin{array}{c} \diagup \text{C}(\text{CH}_2\cdot\text{CO}_2\text{H}) \\ \diagdown \text{NH} \end{array}$   $\text{CH}$ . Many animal hormones

have similar effects. *Kögl* has made an examination of derivatives of indole-carboxylic acid in order to obtain evidence as to relationships between structure and physiological activity (Rep., 1935, 428).

The 3-propionic acid exists in *d*- or *l*-forms, and the former is physiologically about 30 times as active as the *l*-form.

It has been shown that  $\beta$ -indoxylacetic acid, and  $\alpha$ -naphthaleneacetic acid in concentration of 1 in 10,000, promote root development in woody cuttings of plants.

**Ethylene.**—This hydrocarbon is a plant stimulant and important in plant metabolism. In minute amounts it favours root growth, the curvature of the stem or leaf, and is used for colouring and ripening fruits—in fact, acts as a plant hormone. It is claimed that it is formed during normal plant growth and escapes into the atmosphere; it is undoubtedly formed during the process of ripening, and 1 part of ethylene in 20 millions of air can be detected by the curvature of young tomato plants. At high concentration it acts as an anæsthetic (Chap. LXV, B.). Other gases which have similar but not so marked properties on plant tissues are propylene, acetylene, and carbon monoxide.

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## LXIX. FERMENTATION AND ENZYME ACTION

## A. Alcoholic Fermentation

*Lavoisier*, 1789, was the first to recognize that alcoholic fermentation consists essentially in the decomposition of a sugar into alcohol and carbon dioxide; and *Gay-Lussac*, 1810, drew attention to the fact that the presence of air appeared to be essential for fermentation and putrefaction to take place. The fact that brewers' yeast is a low form of plant life was discovered independently by *Cagniard-Latour*, *Theodor Schwann*, and *Kützing*, 1837. By microscopical examination they observed the growth of the organism, and showed that it could be destroyed by heat or by certain poisons. These results were not accepted by *Berzelius*, *Liebig*, and others, who still regarded yeast as a chemical substance without life. According to *Berzelius*, the yeast acted as a contact substance which decomposes the sugar without undergoing change itself; whereas *Liebig* regarded the ferment as an extremely susceptible substance which undergoes a change of the nature of decay, and suggested that the decomposition of the sugar was a type of sympathetic reaction induced by the change of the ferment. In 1857 *Pasteur* began his researches on fermentations. He was able to show that in other cases of fermentation, such as the lactic fermentation of milk, micro-organisms are present. He was further able to show that during alcoholic fermentation the yeast grows and multiplies, and was led to the conclusion that fermentation is a physiological process accompanying the life of the yeast.

In his own words: "I am of opinion that alcoholic fermentation never occurs without simultaneous organization, development, multiplication of cells, or the continued life of cells already formed." This conclusion harmonized with the facts already known that boiled liquids could be kept from fermenting by heating, or filtering through cotton wool, the air admitted to the liquid.

It was *Pasteur* who proved that only 95 per cent of the glucose is accounted for as carbon dioxide and alcohol; he was able to isolate glycerol and succinic acid from the final products.

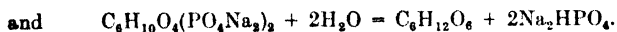
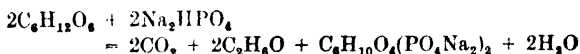
As early as 1858 *M. Traube* expressed the view that all



fermentations produced by living organisms are ultimately due to protein-like ferments, which are definite chemical substances manufactured in the cells of the organism. *Traube's* conclusions were verified in the case of alcoholic fermentation by *Büchner's* isolation of "zymase" from yeast (see p. 85). *Büchner's* yeast juice, when quite free from yeast cells, can ferment solutions of glucose, fructose, sucrose, and maltose. The fermenting power is not destroyed by the addition of chloroform, benzene, or sodium arsenite, antiseptics which inhibit the action of living cells, by filtration through a Berkefeld filter, by evaporation to dryness at 30°-35°, or by precipitation with alcohol. The fermenting power is, however, completely destroyed by heating to 50°, or by the addition of powerful antiseptics. The activity of the juice diminishes with time, as a proteolytic enzyme is also present which gradually decomposes the zymase. Both in rate of fermentation and in the total fermentation produced, the extract or juice is much less efficient than the equivalent amount of living yeast, and glycerol is formed as a by-product when the extract is used. During fermentation a portion of the sugar is converted into a compound of less reducing power which is not fermented, but which yields sugar when hydrolysed with acids. Permanent preparations containing zymase can be obtained by evaporating the juice to a syrup at 20°-25°, drying at 35°, and then exposing to sulphuric acid in a vacuum desiccator. Such a powder when dry retains its activity for twelve months, and can be heated at 85° for eight hours without any serious loss of fermenting power. Another preparation can be obtained by bringing the juice into 10 volumes of acetone, centrifuging, washing the precipitate with acetone and then with ether, and drying over sulphuric acid. An important medicinal preparation known as *zymin* is manufactured by stirring moist yeast with acetone, filtering and draining at the pump, again mixing with acetone and draining. The product is then roughly powdered, kneaded with ether, filtered, drained, and spread on filter paper or porous plates, and finally dried at 45° for twenty-four hours. This product is quite incapable of growth or reproduction, but produces fermentation and is much more active than yeast extract.

The researches of *Harden and Young* (Abs., 1905, ii., 109; 1906, i., 470) indicate that the activity of yeast juice or extract is due to an enzyme and a co-enzyme, which can be

separated by filtration or dialysis through a Martin gelatin filter; the residue contains the enzyme and the filtrate or dialysate the co-enzyme. Neither by itself can induce fermentation, but a mixture of the two is equal in activity to the original juice. The co-enzyme is dialysable, and is not destroyed by boiling, but disappears from yeast juice during fermentation, or when the juice is allowed to undergo autolysis. It cannot be a protein, and its nature has not yet been determined. It is decomposed by acid or alkaline hydrolysing agents, by repeatedly boiling the extract, and also by the lipase of castor beans. In the case of other fermentations brought about by enzymes, e.g. lipase, it has been demonstrated that both enzyme and co-enzyme are necessary, and also that the co-enzyme is a salt of the complex taurochloric acid (p. 227). For other co-enzymes, cf. C.I., 1942, 388. *Harden and Young* (Abs., 1908, i., 590; Bio. J., 1927, 1216) have also shown that phosphates added to a mixture of glucose and yeast juice produce both an initial acceleration and also an increased total fermentation. An optimum concentration of phosphate exists which produces a maximum initial rate of fermentation; an increase beyond this optimum diminishes the rate. The reaction between the glucose and phosphate is represented by the following equations:



According to the first a hexose-diphosphoric acid is formed, and this is then hydrolysed by the water and yields sodium phosphate, which can then react with a further quantity of glucose. These conclusions are supported by the following facts. Careful experiments have shown that during the period of increased fermentation the amounts of alcohol and carbon dioxide produced exceed those which would have been formed in the absence of added phosphate by a quantity exactly equivalent to the phosphate added in the ratio  $\text{C}_2\text{H}_5\text{O}:\text{Na}_2\text{HPO}_4$ . (Compare also *Iwanoff*, Abs., 1909, 1, 752.) It has been proved that the metallic phosphate is not the co-enzyme already mentioned, as the filtered enzyme and phosphate are not capable of inducing fermentation in the absence of the filtrate. Fermentation does not proceed in the absence of phosphate although both

enzyme and co-enzyme are present, and although arsenates and arsenites have accelerating actions on the rate of fermentation they cannot be used in place of the phosphate. The function of the arsenate or arsenite appears to be to act as accelerators in the decomposition of the glucose phosphate. *Slator* finds that phosphates have not an accelerating effect when living yeast cells are employed. He has estimated (J. C. S., 1906, **89**, 128; 1908, **93**, 217) the amounts of carbon dioxide evolved during given periods of time when yeast itself is used, and finds that the rate of fermentation is exactly proportional to the amount of yeast present, and is almost independent of the concentration of the glucose.

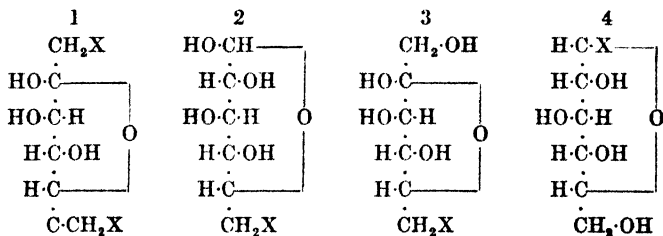
Several hexose-phosphates have been isolated; these include:

1. *Harden* and *Young's* diphosphate, viz. 1:6-fructofuranose diphosphate. It accumulates in minced muscle on inoculation with glycogen in presence of fluorides or iodoacetic acid.

2. *Robinson's* glucopyranose-6-monophosphate, also isolated from yeast juice.

3. *Neuberg's* fructofuranose-6-monophosphate by partial hydrolysis of 1 (1918).

4. *Cari's* phosphate (1936) from washed minced muscle and probably glucopyranose-1-phosphate.



Where X = ·O-PO<sub>3</sub>H<sub>2</sub>.

2 and 3 tend to pass into an equilibrium mixture containing 30 per cent of 3 and 30 of 2, and is sometimes termed *Embden's* hexosephosphate.

Other complex phosphoric acids play an important part in animal physiology; two of these have been isolated, viz. creatinephosphoric acid and argininephosphoric acid, usually termed **Phosphagens**. The latter is hydrolysed on contraction

of a muscle and is reformed during the aerobic recovery phase. For summary of function of organic phosphates in the conversion of glucose and glycogen into pyruvic acid, &c., cf. *Ochoa, C. and I., 1938, 720.*

A yeast which can ferment glucose does not necessarily ferment an isomeric sugar, e.g. galactose; it is probable that different enzymes are required for the different sugars.

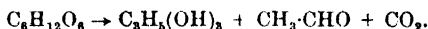
Alcoholic fermentation can take place in three different ways according to conditions:

(a) Normal in fairly acid media; over 90 per cent yields

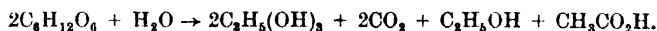


probably through stages (cf. below).

(b) In the presence of sulphites,



(c) Under feebly alkaline conditions, e.g. in presence of  $NaHCO_3$ ,



The fermentation of glucose undoubtedly consists of a whole series of chemical reactions; at present we know the substances we start with and the final products obtained. Several suggestions have been made with regard to the nature of some of the intermediate products. *Büchner* and *Meisenheimer* (B., 1905, 620) have suggested that lactic acid (p. 246), a product also formed in muscle tissue by oxidation of the sugar glycogen, is first formed by the action of zymase on glucose, and that a second enzyme, lactacidase, then decomposes the lactic acid into ethyl alcohol and carbon dioxide; cf. *Bio. Z.*, 1922, 128, 144; 132, 165. This suggestion was based on the fact that a concentrated solution of glucose with alkali yields about 3 per cent of alcohol on exposure to sunlight, whereas a more dilute solution under similar conditions gives a 50-per-cent yield of lactic acid.

Another suggestion is that dihydroxy-acetone,  $CO(CH_2 \cdot OH)_2$ , is an intermediate product, and it has been proved that this compound can be fermented by yeast (*Büchner* and *Meisenheimer*, B., 1910, 1773; *Lebedew*, 1911, 2932; compare also *Franzen* and *Steppuhn*, *ibid.* 2915). The formation of dihydroxy-acetone and glyceraldehyde from *d*-fructose is readily explicable, as the latter is formed by the condensation of the

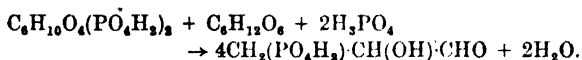
former compounds under certain conditions (p. 354), and in all probability the reaction is a reversible one. It has also been suggested that glyceraldehyde, by the loss of water, yields the enolic form of methyl-glyoxal,  $\text{CH}_2:\text{C}(\text{OH})\cdot\text{CHO}$  and from methyl-glyoxal either lactic acid or even alcohol and  $\text{CO}_2$  can be formed by the addition of water. It is improbable that methyl-glyoxal or lactic acid are important intermediate products in the process of alcoholic fermentation, as they are unacted upon by yeast and yeast juice (*Slater, and Büchner, and Meisenheimer*).

*Neuberg*, 1911, has shown that yeast contains an enzyme, **carboxylase**, which is capable of eliminating  $\text{CO}_2$  from  $\alpha$ -ketonic acids, and suggests that pyruvic acid (p. 256) is an intermediate product in the formation of alcohol, the carboxylase decomposes the pyruvic acid into acetaldehyde and  $\text{CO}_2$ , and the aldehyde is reduced by the yeast to ethyl alcohol. It has been proved that the addition of pyruvic acid to the fermenting liquor in the presence of glycerol, which may act as an enzyme preservative, increases the yield of alcohol, and it is also known that yeast contains enzymes capable of reducing aldehydes (p. 727).

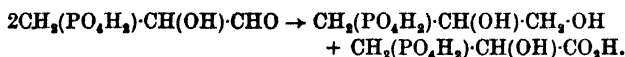
More recent work by *Embden* and by *Meyerhoff* (*Bio. Z.*, 1933, **260**, 417; **264**, 40) supports the view that pyruvic acid is an important intermediate, but proves that methyl-glyoxal is not formed. The work emphasizes the importance of hexose-phosphates in the changes, which can be represented as recurring in the stages:

(1) Glucose  $\rightarrow$  glucose diphosphate (cf. p. 1238).

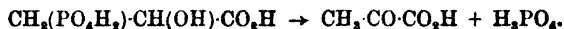
(2) Glucose diphosphate + glucose + phosphoric acid  $\rightarrow$  glyceraldehyde monophosphate,



(3) The glyceraldehyde phosphate yields the monophosphates of glycerol and glyceric acid,

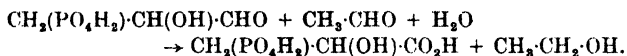


(4) The latter yields pyruvic and phosphoric acids,



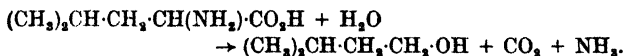
(5) With carboxylase the pyruvic acid yields acetaldehyde and carbonic anhydride (cf. above).

(6) In normal (acid) alcoholic fermentation the acetaldehyde reacts with glyceraldehyde monophosphate (cf. 2), yielding by addition of water ethyl alcohol and glyceric acid monophosphate,



The actual formation of acetaldehyde during fermentation can be proved by adding a compound which can fix aldehydes, e.g. bisulphite or dimethyldihydroresorcinol.

Of the by-products mentioned on p. 85, glycerol is formed from the sugar, as *Büchner* and *Meisenheimer* have shown that it is also formed when yeast extract or zymin acts on sugar solutions. As stated on p. 229, the yield of glycerol can be increased to 25 per cent or more of the weight of the sugar by using suitable yeasts in the presence of sodium carbonate or sulphite. The fusel oil and succinic acid, on the other hand, do not owe their origin to the sugar, but to other products present in the mixture undergoing alcoholic fermentation. The researches of *F. Ehrlich* (1904-10) prove that the alcohols and also the aldehydes present in ordinary fusel oil are derived from the amino-acids formed by the hydrolysis of proteins. Thus isoamyl alcohol, one of the chief constituents of fusel oil, is closely related to leucine ( $\alpha$ -amino-isohexanoic acid), and active amyl alcohol to isoleucine ( $\alpha$ -amino- $\beta$ -methyl-valeric acid), both of which are formed by the hydrolysis of proteins, and according to *Ehrlich* both these acids are transformed into the corresponding amyl alcohols under the influence of pure yeast cultures, in the presence of sugar:



These changes, although brought about by yeast, do not occur when zymin or yeast extract is used. Other amino-acids undergo a similar decomposition: tyrosine (p. 526) yields *p*-hydroxy-phenyl-ethyl alcohol, tyrosol,  $\text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$ , and phenyl-alanine (p. 521) gives phenyl-ethyl alcohol.

The ammonia is not found at the end of the reaction, as it is used up by the organism for the purpose of building up new protein molecules. If appreciable amounts of simple

nitrogenous substances, such as ammonium salts, are originally present in the fermenting liquor, the organism uses these in preference to decomposing the amino-acids; and *Ehrlich* has found it possible to increase or diminish the amounts of fusel oil formed, by diminishing or increasing the amounts of ammonium salts present at the beginning of the fermentation, and also to increase the fusel oil by the addition of larger amounts of amino-acids to the fermenting mixture (cf. Chap. LXI, A., Rubber). Practically all amino-acids formed by the hydrolysis of proteins can undergo similar decomposition by yeast, but only in the presence of sugar. The succinic acid found as a by-product in alcoholic fermentation is probably formed in a similar manner from glutamic acid.

According to *Neuberg* and *Fromherz* (1911), ketonic acids are probably formed as intermediate products in the fermentation of amino-acids to alcohols; and *Neuberg* has been able to show that many  $\alpha$ -ketonic acids, e.g. pyruvic,  $\text{CH}_3\cdot\text{CO}\cdot\text{CO}_2\text{H}$ , and oxalacetic,  $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CO}_2\text{H}$ , are readily decomposed by yeast even in the absence of sugar, yielding carbon dioxide and aldehyde (cf. p. 1240). With a 1-per-cent solution of pyruvic acid the decomposition is almost as rapid as with a sugar solution.

*Pasteur's* view that yeast will thrive in a solution of glucose with small amounts of suitable salts, such as ammonium salts and phosphates, holds good for wild yeasts only. A highly cultivated yeast requires the addition of a small amount of wort, which contains the hormone *bios*, which has since been shown to be a mixture of meso-inositol, aneurin (Chap. LXVIII, A.), and a compound *biotin*, probably  $\text{C}_{11}\text{H}_{18}\text{O}_3\text{N}_2\text{S}$ .

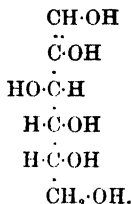
In alcoholic fermentation the percentage of alcohol cannot exceed a maximum of 14 per cent, but if the conditions are such that the alcohol is removed as it is formed, e.g. continuous washing with amyl alcohol, higher concentrations of glucose can be used and the whole fermented.

With the wild yeast *Torula utilis* in presence of air, alcoholic fermentation does not occur but oxidation, and the sugar yields  $\text{CO}_2$  and  $\text{H}_2\text{O}$ .

Of all the known hexoses—natural and synthetic—only four are fermentable by yeasts, viz. the *d*-forms of glucose, mannose, galactose, and fructose, all of which occur in nature.

A species of yeast which ferments one of the three, viz. glucose, mannose, and fructose, will ferment the other two,

and at approximately the same rate and with the same temperature coefficient. Characteristic of the four sugars mentioned is the common enolic form:



In fermentation probably the same hexose-phosphate is formed in all four cases.

Methyl glucoside, glucosone, gluconic acid are not fermentable, and it is not possible for them to yield the enolic form given above.

Galactose is fermented much more slowly, and certain yeast species will not ferment it at all. Talose and tagatose (a ketose), although they contain the same configuration as galactose with respect to C atoms 3, 4, and 5, are not fermented. No pentose is fermentable by yeast, nor yet any synthetic tetrose, heptose, or octose, whereas a synthetic nonose obtained by cyanhydrin synthesis from mannose and a keto-triose (dihydroxyacetone) is.

Types of other fermentations have already been referred to (cf. pp. 174, 177, 246).

## B. Fermentations by Bacteria

Butyl alcohol fermentation of starch, usually in the form of maize mash, by means of a bacterium termed *Clostridium acetobutylicum*. The products are *n*-butyl alcohol, acetone, carbon dioxide and hydrogen, and the proportions roughly those represented by the equation:



the primary products are probably acetic and butyric acids and oxygen, which oxidizes the butyric to acetoacetic acid and hydrogen, or there is simultaneous oxidation and reduction of two molecules of butyric acid by  $2\text{H}_2\text{O}$ , i.e.  $4\text{H} + 2\text{O}$ . (For details of process, see Ind. Eng., 1927, 46, 1147.)

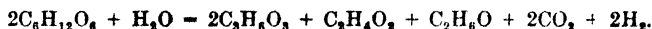


Bacteria are much more sensitive to deterioration than yeasts, and hence fresh cultures must be used, and all foreign organisms in the medium must be destroyed by sterilization before adding the organism. The optimum temperature is  $37.5^{\circ}$ , with  $p_H$  4.3, and the fermentation is complete in 2-3 days. The yields of products can be altered by the addition of suitable acids or bases to the mash, e.g. addition of calcium carbonate favours the formation of butyric and acetic acids. The hydrogen, after washing and removal of  $CO_2$  by solution in water under pressure, is remarkably pure and can be used for purposes of catalytic hydrogenation (Chap. XLIX, A.), or a mixture of the two gases can be catalytically converted into methanol (Chap. XLIX, B.),  $CO_2 + 3H_2 \rightarrow CH_3 \cdot OH + H_2O$ .

By using *C. Pasteurianum* (Winogradsky) a 32-per-cent yield of products is obtained containing acetone 8, *n*-butyl alcohol 67, and ethyl and isopropyl alcohols 25 per cent.

**Cellulose Fermentation.**—Cellulose can be fermented by certain heat-resistant organisms obtained from steaming stable manure. They grow most rapidly at  $60^{\circ}$ - $68^{\circ}$  and, according to Langwell (C. and I., 1932, 988), by varying the conditions the following products can be obtained: acetic acid, butyric acid, lactic acid, alcohol, hydrogen, carbon dioxide, methane. Under suitable conditions the yields of acetic and butyric acids can reach 58 per cent of the dry cellulose used, and the method can probably be utilized for the manufacture of acetic acid.

According to Harden (J. C. S., 1901, 610), *Bacillus coli communis* ferments glucose, fructose, or mannitol, yielding lactic, succinic, and acetic acids, alcohol, formic acid, carbon dioxide, and hydrogen. The main reaction can be represented by the equation:



With glucose the weight of lactic acid is practically 50 per cent of the sugar, and the alcohol and acetic acid are formed in equal amounts. The alcohol probably comes from the group  $CH_2(OH) \cdot CH(OH)$ , and as this group occurs twice in the molecule of mannitol the yield of alcohol is much greater when this compound is used. The lactic acid is probably derived from the  $CH(OH) \cdot CH(OH) \cdot CH(OH)$  grouping. *B. typhosus* yields similar products, except that it gives formic

acid instead of carbon dioxide and hydrogen (Abs., 1906, II., 380).

**Oxidizing Bacteria.**—*B. xylinum* (sorbse bacterium) oxidizes certain aldoses to aldonic acids, ( $\cdot\text{CH}:\text{O} \rightarrow \cdot\text{CO}\cdot\text{OH}$ ), e.g. glucose, galactose, xylose, and arabinose. It can also oxidize certain alcohols to ketoses, ( $\cdot\text{CH}(\text{OH})\cdot \rightarrow \cdot\text{CO}\cdot$ ), e.g. mannitol to fructose and sorbitol to sorbose, also erythritol and arabitol, but not dulcitol or xylitol. The  $\cdot\text{CH}(\text{OH})\cdot$  oxidized must be adjacent to  $\cdot\text{CH}_2\cdot\text{OH}$  on one side and to another  $\cdot\text{CH}(\text{OH})\cdot$  on the other, so that the two OH groups are *cis* to one another. Strains of *aceto-bacterium* can also bring about oxidation of aldoses. *B. mesentericum* can oxidize mannitol to mannose and dulcitol to galactose. Gluconic acid is now manufactured from 25-per-cent glucose solutions containing small amounts of nitrogenous compounds by *B. oxydans*, *B. aceti*, and other varieties at  $15^\circ$ – $35^\circ$ , and the yield can reach 100 per cent. Dihydroxyacetone,  $\text{OH}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{OH}$ , is formed in large quantities by the oxidation of glycerol with *B. suboxydans* in 15-per-cent solution with strong aeration and a  $p_{\text{H}}$  value 6.5, falling to 4.5 at  $30^\circ$ .

### C. Fermentations by Moulds \*

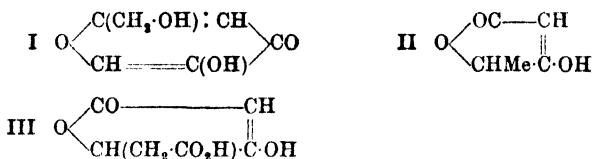
Examples of oxidative changes are acetates to oxalates by *Mucor stolonifer*; glucose to gluconic or citric acid by *Aspergillus niger*, *Penicillium luteum*, and particularly *P. purpurogenum* at  $3^\circ$ – $15^\circ$ . Citric acid is now produced on a large scale by the action of *A. niger* on glucose solutions (20 per cent) containing nutrient salts with the addition of calcium carbonate. In one factory some nine acres of the mycelium are kept in operation. The yield is as high as 87 per cent, but the fermenting power of the organism decreases with time and must be revived by growth on a suitable nutrient medium. The various chemical changes have not been determined.

An extremely interesting reaction is the reduction of glucose to *d*-mannitol by means of species of *Aspergillus*, with yields of 50 per cent of the sugar fermented. When reduced chemically glucose yields, as a rule, the stereoisomeric sorbitol.

Several cyclic compounds, e.g. *kojic acid*, 5-hydroxy-2-

\* Clutterbuck, J. S. C. I., 1936, 55 T.

hydroxymethyl- $\gamma$ -pyrone (I);  $\gamma$ -methyltetronic acid (II), and derivatives of  $\gamma$ -tetronylacetic acid (III), are formed from



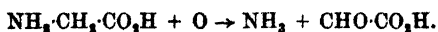
mono- and poly-saccharides with species of *Aspergillus*, and No. III with *Penicillium Charlesii*. The last are interesting as they are related to ascorbic acid (Chap. LVI, E.).

Numerous aromatic compounds, including hydroxyanthraquinone pigments, can be formed with the aid of species of *Penicillium*, *Aspergillus*, and *Helminthosporum*, e.g. 2-methyl-4:5:8-trihydroxyanthraquinone (helminthosporin); with the aid of *H. gramineum*, which is the cause of leaf-stripe disease of barley. *P. griseofulvum* yields 6-hydroxy-2-methylbenzoic acid and gentisic acid (2:5-dihydroxybenzoic acid), and *P. brevicompactum* yields 3:5-dihydroxyphthalic acid.

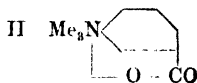
Moulds are capable of synthesizing poly-saccharides from hexoses, e.g. *A. niger* and *P. variable* yield mould starch, species of *Aspergillus* form glycogen, and *P. Charlesii* yields polygalactose and polymannose.

Moulds can also synthesize fats, complex fatty acids, and sterols. Ergosterol (Chap. LXII, C.) is now manufactured by these organisms.

**Methylation by Moulds.**—The investigations of *Challenger* and his co-workers (J. C. S., 1933, 95; 1934, 68; 1935, 396; 1936, 264; C. and I., 1935, 657; 1936, 155, 900; 1937, 838) show that media containing starchy material and inorganic or organic derivatives of arsenic or selenium or aliphatic mercaptans or disulphides can, in the presence of *P. brevicaulis*, yield trimethylarsine or methyl derivatives of Se and S; thus EtSH yields EtMeS, and (EtS)<sub>2</sub> yields MeEtS. The poisoning caused by damp wallpapers containing arsenical pigments is due to the formation of AsMe<sub>3</sub> and not AsH<sub>3</sub> as first suggested. When ethylarsenic acid is present the product is EtMe<sub>2</sub>As. It is suggested that the methylation may be due to the formation of CH<sub>2</sub>:O or CO<sub>2</sub>H·CHO (glyoxylic acid) by the deamination of glycine,



Methylations can also occur in the animal system; thus pyridine and quinoline are respectively converted into methylpyridinium and methylquinolinium hydroxides in the dog, probably through the agency of glyoxylic acid. Nicotinic acid (I) yields trigonelline (II):



## D. Enzyme Action \*

Attention has been drawn several times (pp. 85, 946) to the fact that chemical decompositions can be brought about by certain complex organic substances found in animal and plant tissues. Such substances are termed *unorganized ferments* or *enzymes*.

### 1. CLASSIFICATION OF ENZYMES

#### 1. Hydrolytic enzymes.

(a) Proteolytic or protein splitting enzymes, e.g. *pepsin*, *trypsin*, *proteases*. For further classification, cf. this Chap., 2.

(b) Lypolytic or fat splitting enzymes, e.g. *lipase* and *esterase*.

(c) Carbohydrate splitting, e.g. *sucrase* (invertase), *maltase*, *lactase*, and glycoside splitting enzymes, e.g. *amygdalin*.

(d) Amylotic or starch splitting, e.g. *amylase* (diastase).

2. Coagulating enzymes, e.g. *thrombase* (thrombin) which assists the clotting of blood, and *rennin* which causes the clotting of milk.

3. Oxidizing enzymes, e.g. *oxidases* and *dehydrogenases*.

4. Reducing enzymes (*reductases*), e.g. yeast can reduce acetaldehyde to alcohol and citral to geraniol.

5. Enzymes which evolve carbon dioxide without using free oxygen, e.g. *zymase* † and *carboxylase* † which evolves CO<sub>2</sub> from pyruvic acid.

6. Splitting enzymes which break down a large into smaller molecules, e.g. the enzyme which produces lactic acid from glucose.

\* *Enzyme Chemistry*, Tauber, London, 1937. *Biological Oxidation*, Oppenheimer, Stern and Roman, The Hague, 1939.

† Both require a co-enzyme. The co-carboxylase has been shown to be a pyrophosphoric ester of aneurin, vitamin B1 (Chap. LXVIII, A.).

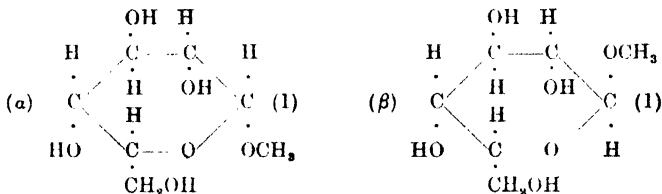
7. Enzymes causing molecular rearrangement (= *mutases*).

The name given to a particular enzyme ends in *ase*, and usually indicates the compound it can decompose. It frequently has a prefix indicating its origin, e.g. malt amylase (old name, diastase), indicating an enzyme which can hydrolyse starch and derived from malt.

The enzymes are of complex colloidal nature, and a solution consists of a dispersion of colloidal particles throughout the liquid phase. Thus they are a type of heterogeneous catalyst, and the action takes place at the intersurface between the colloidal enzyme and the substrate solution. Probably no enzyme has been isolated in a pure state. They can be concentrated by processes of dialysis to remove crystalloid impurities, by fractional precipitation, and also by selective absorption on electro-positive material, e.g.  $\text{Al}(\text{OH})_3$ , or electro-negative material, e.g. kaolin, and by such methods products with a high degree of activity can be obtained. In some respects they resemble the inorganic metallic and metal oxide catalysts. They are sensitive to heat, much more so than the inorganic catalysts, and each enzyme has a characteristic optimum temperature. For most enzymes this lies between  $25^\circ$  and  $38^\circ$ , but a few which decompose cellulose have an optimum of  $68^\circ$ – $70^\circ$ . As a rule there is little activity at  $0^\circ$ , and in most cases activity is destroyed by raising the temperature to  $70^\circ$ – $100^\circ$ , probably due to the coagulation of the enzyme, i.e. the destruction of the interface. Enzymes can be poisoned. They are fairly resistant to certain antiseptics which kill fermenting organisms, but their activity can be destroyed by stronger agents such as formaldehyde. These are spoken of as *anti-enzymes*. In the living body an enzyme often forms anti-enzymes, which tend to oppose the action of the enzyme, and even proteins will retard the action of some enzymes. There are other substances which act as stimulants or promoters—usually termed *co-enzymes*—and one of these has been described in connexion with zymase.

The **selective** character of enzymes is far more pronounced than that of inorganic catalysts; the activity of a given enzyme may be restricted to a group of allied compounds or even to a single substance, and in this respect they differ from mineral acids, which act as general catalysts. An example of the former type is lipase (from castor seeds or liver), which hydrolyses glycerides and many types of esters but cannot hydrolyse

complex carbohydrates. Maltase is of the latter type, as it hydrolyses maltose but not sucrose. (See also Proteolytic Enzymes.) Even a slight difference in the configuration of two isomeric substances is sufficient to affect their reactivity with a particular enzyme, e.g. the two methyl-glucosides (pp. 340 and 911) which are represented by the spatial formulæ:



the only difference being the arrangement of the H and OCH<sub>3</sub> attached to the carbon atom (1). Of these two compounds the  $\alpha$  can be hydrolysed by maltase but not by emulsin, and the  $\beta$  by emulsin but not by maltase, and hence the names  $\alpha$  and  $\beta$  glucase are sometimes used for the two enzymes maltase and emulsin. So specific are the activities of the hydrolysing enzymes that practically each di-, tri-, or polysaccharose has its own enzyme, which frequently accompanies it in the plant or animal tissue. The enzyme does not always exist as such in the tissue; sometimes it is present as a zymogen which forms the enzyme in presence of a suitable reagent, usually an acid.

Inulase hydrolyses inulin; cellulase (or cytase), cellulose; lactase, lactose; melibiase, melibiose, &c.

Similarly, each of the natural glycosides described in Chap. LVI, F., is accompanied in the plant by its own enzyme; and as most of them are hydrolysed by emulsin but not by maltase, they are regarded as analogous to the  $\beta$ -methylglucoside, with complex radicals in place of the methyl group. Maltose, on the other hand, is an  $\alpha$ -glucoside resembling the  $\alpha$ -methyl compound in configuration. Invertase is probably a mixture of two enzymes, one of which is attracted to the glucose and the other to the fructose portion of the sucrose molecule. A biose need not necessarily be hydrolysed to a monose before fermentation by yeast, since maltose can be fermented by maltase free yeast. Alkylglycosides derived from non-fermentable sugars, e.g. pentoses and heptoses, are not attacked by either  $\alpha$ - or  $\beta$ -glucase.

The hydrogen ion concentration of the substrate is an important factor, and for each enzyme a critical concentration exists and is denoted in terms of  $p_H$ , i.e. the log of the reciprocal of the  $H^+$  concentration. For pure water  $H^+ = OH^- = 1/10^{7.07}$ , i.e. the  $p_H$  for water is 7.07. For acid media, i.e. high  $H^+$  concentration, the values of  $p_H$  lie between 7.07 and 0, and for alkaline media between 7.07 and 14.14.

Theoretically a small amount of an enzyme should be capable of decomposing unlimited amounts of substrate; the relative proportions are very high, e.g. 1 : 4 millions, but is not unlimited, as the enzyme itself, probably a protein derivative, undergoes hydrolysis and hence its concentration diminishes, and, at the same time, the products of hydrolysis tend to retard the reaction and to produce a state of equilibrium, as the reaction, in most cases, is reversible.

A few only of the enzymes have been obtained crystalline, viz. urease, pepsin, and trypsin, and these show many of the properties characteristic of proteins. It has been suggested that each enzyme has two characteristic groups: one of these facilitates the union between enzyme and substrate, and the other causes the splitting of this compound into enzyme and decomposition compounds.

## 2. PROTEOLYTIC ENZYMES

**I. Proteinases or Endopeptidases.** As a rule these hydrolyse only relatively complex proteins and not simpler polypeptides.

*Pepsin*, secreted by stomach.

*Trypsin*, secreted by pancreas: probably several.

*Cathepsin*, an intercellular enzyme in liver and kidney.

*Papain*, present in fruit of *Carica papaya* (papaw tree).

*Bromelin*, present in pineapple.

Characteristic of these is they split complex peptides in the middle of the chain and at peptide links.

**II. Peptidases or Exopeptidases.**

(a) Hydrolyse  $\cdot CO \cdot NH \cdot$ , but not  $\cdot CO \cdot N <$  grouping.

(1) With an additional activating group near the peptide link, e.g.

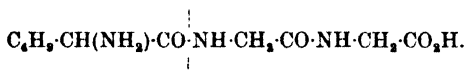
*Carboxypeptidases*, from pancreas, yeast, and moulds. *Aminopeptidases*, from intestinal mucosa, yeast, and moulds.

(2) With two activating groups near the peptide link, e.g.

*Prolinase*, from intestinal mucosa and yeast. *Dipeptidase*, from the same, also liver, kidney, and moulds.

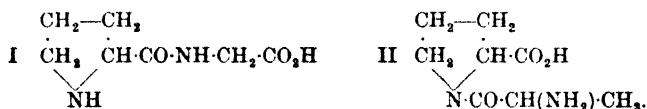
(b) Hydrolyse  $\cdot\text{CO}\cdot\text{N}<$ , but not  $\cdot\text{CO}\cdot\text{NH}\cdot$  grouping.

Characteristic of the proteinases is the fact that they can hydrolyse (split) at a peptide link with no  $\text{CO}_2\text{H}$  or  $\text{NH}_2$  adjacent to it; in fact, the presence of such groups hinders fission (*Bergmann* and others, *J. biol. C.*, 1935, **111**, 225; 1937, **117**, 189; **118**, 405). With a carboxypeptidase it is essential that a peptide link in the protein should have an adjacent  $\text{CO}_2\text{H}$  group, and fission occurs at the peptide link adjacent to this group. Similarly, an amino group is essential for an aminopeptidase to function, and fission occurs at the peptide link nearest to this amino group, e.g.



Fission occurs at the point indicated, whereas with a carboxypeptidase it would occur at the other peptide link, viz. adjacent to the  $\text{CO}_2\text{H}$ . A polypeptide of the type  $\text{CH}_3\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}\cdot\text{NMe}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  is not hydrolysed by aminopeptidases owing to the presence of the NMe group in place of NH.

Prolinase will hydrolyse I and another prolinase can split II:



A dipeptidase will split dipeptides only, and requires both a free  $\text{CO}_2\text{H}$  and a free  $\text{NH}_2$  group, and requires H atoms attached to the C atoms  $\alpha$  to both  $\text{CO}_2\text{H}$  and  $\text{NH}_2$  and also to the N of the peptide link, e.g.  $\text{NH}_2\cdot\text{CHR}'\cdot\text{CO}\cdot\text{NH}\cdot\text{CHR}\cdot\text{CO}_2\text{H}$ , and the peptide must be of the type where the  $\alpha$   $\text{NH}_2$  group of one molecule forms the peptide link with the  $\alpha$   $\text{CO}_2\text{H}$  group of another molecule. If the  $\text{NH}_2$  or  $\text{CO}_2\text{H}$  is not  $\alpha$  to the peptide link, splitting does not occur, e.g.  $\beta$ -l-aspartyl-l-tyrosine,



It is essential that the amino-acids forming the dipeptide should be the same optically active forms as occur in nature. If built up of the enantiomorphs, fission does not occur.



Many of the older enzymes, e.g. the diastase of malt (p. 86), have been shown to be mixtures; thus this enzyme contains at least three components, viz.  $\alpha$ -amylase,  $\beta$ -amylase, and a phosphatase; the last of these hydrolyses the small amounts of phosphate ester groups, producing liquefaction but does not form sugars. The  $\alpha$ -amylase attacks the middle of the starch molecule, forming products of medium size, whereas the  $\beta$ -amylase attacks the ends of the molecule, splitting off maltose step by step.

### 3. SYNTHETIC FUNCTIONS OF ENZYMES

In the majority of cases the enzyme action is reversible, so that a disaccharide can be synthesized from a hexose by means of certain enzymes, and a lipase can not only promote the hydrolysis of a glyceride but can also build it up from fatty acid and glycerol. The process of hydrolysis is thus a balanced reaction, although in the majority of cases the equilibrium is mainly in the direction of analysis and not synthesis, and synthesis is favoured by using only small amounts of water. The synthesizing activity of an enzyme was first demonstrated by *Croft-Hill* (J. C. S., 1898, 634; 1903, 578) in the case of maltase. The greater portion of the maltose is hydrolysed to glucose, but a certain proportion of disaccharide is always present, and in a solution of glucose maltase can produce a certain amount of a disaccharide, **revertose**, which at first was thought to be maltose, but has since been proved to be isomeric and probably a mixture (*Georg and Pictet*, *Helv.*, 1926, 612). The formation of starch in plant and glycogen in animal tissues is probably largely due to the activities of synthesizing enzymes; and *Potterin* has succeeded in synthesizing a triolein, one of the common constituents of natural fats, by means of a lipase.

*Bourquelot* and his co-workers (*Annales*, 1913 (viii), 28, 145) have synthesized numerous  $\beta$ -glucosides and  $\beta$ -galactosides by means of  $\beta$ -glucase (emulsin). As the reaction is reversible, it is advisable to reduce the amount of water and to work in the presence of an appreciable excess of alcohol or other hydroxylic compound which is to form the glucoside with the dextrose. The following  $\beta$ -compounds have been synthesized: methyl-glucoside, geranylglucoside, cinnamylglucoside, and benzyl-glucoside, most of which are definite crystalline compounds

which are readily hydrolysed by  $\beta$ -glucase in the presence of water.  $\alpha$ -Glucosides and galactosides have been synthesized by means of an enzyme ( $\alpha$ -glucase) present in the aqueous extract from bottom yeast (*ibid.* 1915 (ix), 3, 28), and  $\alpha$ - and  $\beta$ -glucosides and galactosides derived from di- and tri-hydric alcohols, e.g. glycol and glycerol, have also been prepared (*ibid.* 4, 310).

Emulsin not only contains  $\beta$ -glucase but also other enzymes, e.g. gentiobiase, cellulase, and  $\beta$ -galactase (C. R., 1915, 161, 463). The best yields of  $\beta$ -alkylglucosides are obtained by using solutions containing about 15–20 per cent of dextrose. With higher concentrations of dextrose and smaller concentrations of alcohol the effects of the gentiobiase and cellulase become apparent, and by the action of emulsin on an aqueous solution of *d*-galactose it has been found possible to isolate a syrupy galactobiose with  $\alpha_D = +54^\circ$  (*ibid.*, C. R., 1916, 163, 60).

The action of invertase (sucrase) on cane sugar appears to be a non-reversible one, and hence the synthesis of sucrose from *d*-glucose and *d*-fructose by this enzyme is not to be expected (*Hudson*, J. A. C. S., 1914, 1571; *Lob. Abs.*, 1916 (i), 296).

It is now generally conceded that a particular enzyme which produces the hydrolysis of a glucoside is the enzyme which is instrumental in synthesizing that glucoside, as the same equilibrium is attained when the reaction is started from either end (C. R., 1913, 156, 957; *Bayliss*, P. R. S., 1912, B., 85, 359).

Certain proteolytic enzymes not only catalyse hydrolysis and also synthesis, but can act as catalysts in bringing about an exchange of terminal amino-acids in a protein (cf. alcoholysis).

The rate of hydrolysis by means of enzymes has been studied by different authorities. Many, e.g. *O'Sullivan* and *Thompson* (J. C. S., 1890, 834) and *Hudson* (J. Am. C. S., 1908, 1160, 1564; 1909, 655), indicated that in the inversion of sucrose by invertase constant values for  $k$  can be obtained by using the ordinary equation for a unimolecular reaction, provided that the complications attending the mutarotation of the glucose and fructose (Chap. LXXI, I2) are avoided by adding a small quantity of alkali before taking the polarimetric reading. The alkali stops the inversion, and at the same time rapidly brings about equilibrium between the  $\alpha$ - and  $\beta$ -glucoses and the  $\alpha$ - and  $\beta$ -fructoses, so that the normal rotatory power of invert sugar is given. *Hudson's* results

clearly prove that the  $\alpha$ -modifications of glucose and fructose are first formed. Compare *Rosanoff, Clerk, and Selby*, J. A. C. S., 1911.

Other results (*Armstrong*, P. R. S., 1904, 1907, 1908, 1910, 1912, 1913) show that if the products of action are removed and no deterioration of enzyme occurs the amount of decomposition per unit time is constant throughout the change, i.e. the hydrolysis-time curve is linear, and this agrees with the conclusion that enzyme and substrate form definite compounds.

A view generally held with regard to the mechanism of enzyme reaction is that adsorption of substrate by the enzyme, followed in some cases by activation at certain centres or even by combination, takes place. The fact that a specific enzyme can hydrolyse only particular substrates is in harmony with this view, as it is known that chemical constitution plays an important part in adsorption. Cf. *H. E. and E. F. Armstrong*, P. R. S., 1913, B., 86, 561.

## E. Food Digestion: Metabolism

The diversity and complex nature of enzyme action is shown in a study of the changes which occur in the alimentary tract. Broadly the process of digestion transforms complexes and colloids which cannot pass through animal membranes into crystalloids which can, e.g. proteins into amino-acids and starch into glucose. Practically all the changes are effected by enzymes and corresponding co-enzymes, and it has been suggested that as many as 100 enzymes may be involved. It is noteworthy that these enzymes work rapidly as compared with mineral acids in hydrolysing carbohydrates. The enzymes involved include those acting on: (a) *Carbohydrates*—(i) *Phyalin* in salivary glands, (ii) *Pancreatic amylase*, (iii) *Sucrase*, (iv) *Maltase*, (v) *Lactase*, all from the intestinal mucosa; (b) *Fats*—*Lipases* from the gastric mucosa and pancreas; (c) *Proteins*—(i) *Pepsin* from the gastric mucosa and yielding proteoses and peptones, (ii) *Trypsin* from the pancreas yielding peptones and polypeptides, (iii) *Erepsin* from the intestinal mucosa, *prolinase* and *dipeptidase* from the same source yielding finally amino-acids. It is noticeable that the various enzymes are found in the portion of the

digestive system where they are required for their own particular type of hydrolysis.

The food is masticated and becomes mixed in the mouth with the faintly alkaline saliva containing ptyalin, digestion begins, and the mixture passes into the upper or cardiac region of the stomach, where it remains at rest and alkaline digestion continues, but it is finally forced into the muscular or pyloric region near the small intestine, where vigorous muscular movement begins some 20-30 minutes after the intake of food. The middle portion of the stomach is distinctly acid, due to the liberation of hydrochloric acid from numerous parietal cells, but becomes neutral or faintly alkaline in the pyloric region. The muscular activity in the middle and pyloric regions produces intimate mixture of the food with the digestive juices and at the same time forces the mixture towards the small intestine. The food remains in the cardiac region for 0.5-2 hours in a faintly alkaline medium, and if sufficient ptyalin is present the starch is converted into maltose and dextrins, but in the middle portion the mixture becomes distinctly acid (0.4 to 0.5 per cent of the juice), the ptyalic activity is stopped, and the proteolytic action of pepsin starts. On the whole proteins remain longer unchanged in the stomach than carbohydrates, and fats longer than proteins. As digestion proceeds the pylorus opens more frequently, and the half-digested food in a semi-fluid condition passes into the small intestine and lies for some time in the curve of the duodenum. Here it receives the pancreatic juice and the juices secreted by the walls of the small intestine, and is subjected to energetic to and fro motion by muscular constriction of the wall muscles, whereby intimate admixture of juices and food ensues and also close contact of the digested products with the absorbing wall membrane, so that the absorbed digested food passes into the veins and lymphatic vessels. As the liquid food passes the pylorus the acid becomes neutralized by the bile, pancreatic and intestinal juices which are alkaline.

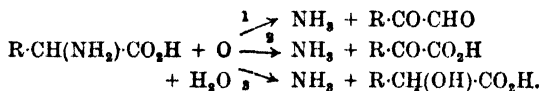
The flow of pancreatic juice is started by the hormone **secretin** (cf. Chap. LXVIII, B.), produced by the action of acid on some constituent of the intestinal mucous membrane; it is absorbed by the blood and carried to the pancreas and stimulates the flow of pancreatic juice. The function of the bile is to facilitate the solution of fatty acids and to diminish

the surface tension between aqueous and oily fluids, permitting the lipase to come into contact with the fatty food. The small intestine contains at least 5 enzymes: enterokinase which converts tripsogenin into trypsin, erepsin, sucrase, maltase, lactase. During 8-23 hours' passage of the products through the small intestine considerable—up to 85 per cent—absorption of digested products occurs. From the small intestine the mass passes into the large intestine and remains there for about 18 hours. During this period there is marked absorption of water and also of products of digestion, and the matrix becomes more and more solid and finally forms fæces. Bacteria are prolific in this area, and it has been estimated that 1 day's food is subjected to the action of 100 billion bacteria.

The monosaccharides, especially glucose, are absorbed by the blood, transferred to the liver and stored there in the form of glycogen (Chap. LVI, D.), and then given up again to the blood as glucose, so that the concentration of this latter is kept fairly constant at 0.1 per cent. The glucose is oxidized to compounds containing three C atoms, e.g. glyceraldehyde, lactic acid, methylglyoxal, and dihydroxyacetone, through the intermediary of phosphate esters (cf. Alcoholic Fermentation, this Chap., A.), and finally to carbon dioxide and water, the energy thus liberated being utilized for muscular energy and for maintaining the body temperature.

When much carbohydrate is formed in the system part is stored as glycogen and part as fat, but the mechanism of fat formation from carbohydrate is not clear. Glucose is partly utilized in forming the lactose of milk.

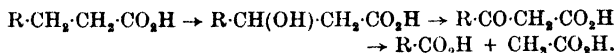
Protein may serve as a source of muscular energy, the amino-acids becoming deamidated by the processes 1-3, and the resulting compounds oxidized:



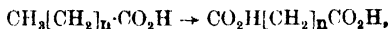
The chief products of digestion are amino-acids, monosaccharides, soaps or fatty acids, and glycerol. Of the monosaccharides glucose is the one most readily utilized, but fructose and galactose can be used in much the same manner. Fructose is converted into glucose in the liver and kidneys of the rat (*Stewart and Thompson, 1939*).

The fatty acids after absorption are reformed into fats or a portion probably into lecithins (glycero-phosphates, Chap. LV, I.) and transported as such, and it has been found that the more unsaturated the fatty food supplied the more unsaturated are the lecithins present in the organism. Fat is stored either for protection or for use later as fuel (depot fat). In the absence of choline fat tends to accumulate in the liver, but normal conditions are restored by the addition of choline to the diet in the form of caseinogen.

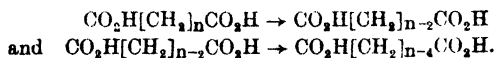
Experiments made by giving saturated fatty acids, their salts or glycerides to dogs prove that these acids can undergo two types of oxidation in the organism: (1)  $\beta$ -oxidation, where carbon atoms are eliminated and a fatty acid with two less carbon atoms formed, probably



(2) Terminal or  $\omega$ -oxidation of the methyl group, resulting in the formation of a dibasic acid,

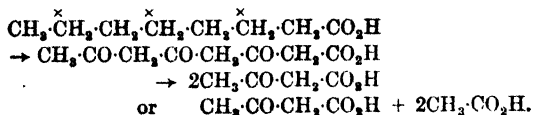


which can then undergo  $\beta$ -oxidation,



An examination of the urine shows that mono- and di-basic acids tend to disappear rapidly as the number of carbon atoms in the acid increases, until with an acid containing 16 C atoms none is excreted as such. In no case can acids containing more than 11 C atoms be isolated from the urine, and the acids actually isolated are those with 10, 8, and 6 carbon atoms when the original acid has an even number of carbon atoms, and 11, 9, and 7 when the original acid has an odd number of carbon atoms (*Verkade, C. and I., 1938, 704*).

*Jowett and Quastel* suggest an alternative to the  $\beta$ -oxidation, viz. the oxidation of alternate  $\text{CH}_2$  groups to  $\text{CO}$ , beginning with the  $\text{CH}_2$  group  $\beta$  to the carboxyl:



This would explain why butyric acid is not an intermediate in the process of oxidation, and why more ketonic bodies are formed from higher acids than from butyric.

Cellulose is of little value in human nutrition, and the small amounts used up are decomposed by intestinal bacteria yielding hydrogen, methane, and fatty acids, and this is the change which occurs with ruminants—largely in the paunch. Lignin, which usually accompanies cellulose, is not digested. Undigested fibre is of value in the human tract as it forms a suitable medium on which the digestive juices and food can come into intimate contact.

Alcohol is extremely rapidly oxidized in the system even before fat or carbohydrate.

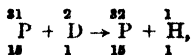
For a list of proteins which cannot be synthesized in the human body and hence must be introduced in the food, see Chap. LXVII, B.

The actual amount of protein required for an adult is a matter of dispute and varies from 40–120 gm. per diem. Excess protein is injurious to the kidneys and leads to excessive formation of uric acid, potassium phosphate, and purine bases. Where rapid output of energy is required, probably a diet rich in protein is an advantage. It is estimated that 0.6–0.7 gm. of phosphorus (in combination) is required per diem by an adult. Other essentials are K, Na, Fe (8–9 mg. per diem), and also traces of Cu and I. Iodine is of importance in cases of cretinism and goitre, and also affects fat and lime metabolism.

## F. Use of Isotopes in Studying Animal Metabolism

Heavy hydrogen (deuterium) and heavy oxygen have been utilized in studying the function of certain compounds in animal metabolism, but the greatest amount of work has been conducted with radio-active phosphorus  $^{32}\text{P}$ . This can be obtained by bombarding  $\text{CS}_2$  with neutrons from a radium beryllium source, and thus forming radio-active phosphorus with a half-life period of 14 days.

It can also be obtained by bombarding red phosphorus with deuterium ions,



which can then be oxidized to phosphate containing ordinary phosphate with some radio-active phosphate, and its path can readily be traced in the animal body. Results prove that when introduced intravenously large quantities are rapidly taken up by the bones, and when practically all radio-active phosphate has disappeared from the blood, it gradually makes its reappearance in the blood by exchange with the bones.

Lecithin cannot exchange ordinary phosphorus for the radio-active variety from active phosphate. If radio-active P is found in lecithin it indicates that the lecithin was synthesized when radio-active P was present, and such facts are useful in deciding in what parts of the body lecithins are formed. They are also of value in studying the formation of phosphate in milk.

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## LXX. POISON GASES

**A. Tear Gases.**—These are mainly aromatic halogen compounds with the halogen in a side chain. Xylyl bromide,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{Br}$ ; xylene bromide,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CHBr}_2$ ; chloroacetophenone,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\text{Cl}$ ; bromobenzyl cyanide,  $\text{Br}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{CN}$ . They all give irritating vapours which affect the eyes.

**B. Nose Gases.**—*Clark I*, diphenylchloroarsine,  $\text{Ph}_2\text{AsCl}$ ; *Clark II*, diphenylcyanoarsine,  $\text{Ph}_2\text{As}\cdot\text{CN}$ ; *Dick*, ethyldichloroarsine,  $\text{EtAsCl}_2$ ; *Adamsite*, diphenylaminechloroarsine. All are strongly irritating to the mucous membrane of the nose, and *Dick* produces asthma.

**C. Choking Gases** affect the lungs and also the eyes. Chlorine, phosgene (p. 315) and its polymer diphosgene (perstoff), chloropicrin (p. 107), trichloroacetaldoxime,  $\text{CCl}_3\cdot\text{CH}:\text{N}\cdot\text{OH}$ , and dichloroformoxime,  $\text{CCl}_2:\text{N}\cdot\text{OH}$ .

**D. Blister Gases.**—*Mustard gas*, or yperite, dichloro-diethyl sulphide (p. 98); *Lewisite*, a mixture of di- $\beta$ -chloro-vinyl-chloroarsine and  $\beta$ -chlorovinyl-dichloroarsine,  $\text{AsCl}\cdot(\text{CH}:\text{CHCl})_2$  and  $\text{AsCl}_2\cdot\text{CH}:\text{CHCl}$ , is prepared from acetylene, anhydrous arsenic trichloride, and aluminium chloride. Mustard gas has an odour of garlic and Lewisite of geranium oil when dilute.



Both have strong blistering action on the skin, especially in the liquid state, and they also affect the lungs.

For detection of these gases, cf. *Studinger*, C. and I., 1937, 225.

## LXXI. RELATIONSHIPS BETWEEN PHYSICAL PROPERTIES AND CHEMICAL CONSTITUTION

### A. Boiling-point

Attention has been repeatedly drawn to the fact that in any homologous series the boiling-point tends to increase with the number of carbon atoms present (see Chap. I, A.; III, A.; VI, A.).

In the majority of cases the increase in boiling-point for each additional  $\text{CH}_2$  is not constant, but tends to decrease with increasing molecular weight (e.g. fatty acids, and especially the paraffin hydrocarbons and alkyl haloids).

In the case of the ethyl esters of the normal fatty acids the increase is fairly constant, and is about  $21^\circ$  for a  $\text{CH}_2$  group (*Kopp*, 1842), e.g.

			Difference
Ethyl formate	..	..	$54.5^\circ \rightarrow 22.5^\circ$
Ethyl acetate	..	..	$77^\circ \rightarrow 21^\circ$
Ethyl propionate	..	..	$98^\circ \rightarrow 22^\circ$
Ethyl butyrate	..	..	$120^\circ \rightarrow 24.5^\circ$
Ethyl valerate	..	..	$144.5^\circ \rightarrow 22.5^\circ$
Ethyl hexoate	..	..	$167^\circ \rightarrow 21^\circ$
Ethyl heptoate	..	..	$188^\circ \rightarrow 20^\circ$
Ethyl octoate	..	..	$208^\circ \rightarrow 20^\circ$
Ethyl nonoate	..	..	$228^\circ$

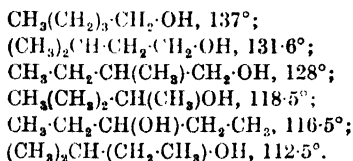
With the alkyl chlorides the difference between methyl and ethyl chlorides is  $35^\circ$ , and this difference diminishes by  $2^\circ$  for each subsequent homologue, so that the difference between heptyl and octyl chlorides is only  $23^\circ$  (*Schorlemmer*).

Attempts have been made to find a general law for the diminution of the difference in boiling-point with increase in molecular complexity. *Goldstein* suggested the formula

$$\frac{n-1}{n} 380 + (n-1) 19 = 340.9^\circ$$

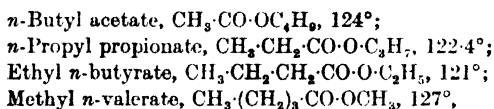
for the boiling-points of the normal hydrocarbons, where  $n$  = the number of carbon atoms; this gives good results up to  $C_{12}H_{26}$ , but not beyond. (Compare also *Mills*, *Phil. Mag.* [5], 17, 180.)

A comparison of isomeric substances shows that the boiling-points can vary considerably, even when the isomerides belong to the same series, e.g. the amyl alcohols:



In all such cases the normal compound has the highest boiling-point, and the more branched the carbon chain becomes, the lower is the boiling-point. Generally there is a difference of  $7^\circ$  between the boiling-points of a pair of isomeric compounds of the type  $CH_3\cdot CH_2\cdot CH_2\cdot X$  and  $(CH_3)_2\cdot CH\cdot X$ . According to *Menschutkin*, in a group of isomeric alcohols, amines, or amides, the boiling-point falls as the side chain approaches the hydroxy- or amino-substituent.

A comparison of isomeric esters, e.g.



shows that the boiling-point is lower the nearer the oxygen atoms are to the middle of the carbon chain.

A remarkable feature is the relatively high boiling-points of hydroxylic compounds when compared with their isomerides or with closely related compounds. As an example, the  $n$ -acid isomeric with the last-mentioned group of esters, namely  $n$ -hexoic acid, boils at  $205^\circ$ . The acid as its dimeride can form a chelate ring. A similar relationship can be shown by the comparison of an alcohol with the ethers isomeric with it. Similarly, a comparison of the boiling-points of the ethyl-derivatives,  $C_2H_6$ ,  $C_2H_5\cdot OH$ ,  $C_2H_5Cl$ ,  $C_2H_5Br$ ,  $C_2H_5NH_2$ ,  $C_2H_5\cdot OEt$ ,  $C_2H_5\cdot CN$ , indicates the enormous effect of the hydroxyl group on the boiling-point, or, again, a comparison

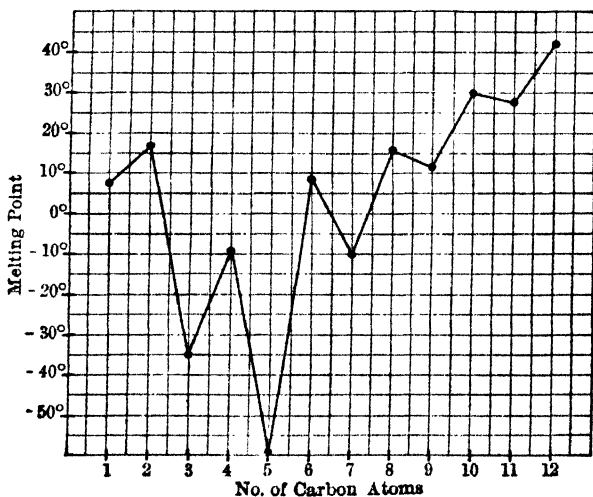
of the boiling-point of an acid with those of its chloride, esters, anhydride, or nitrile.

The effect of the introduction of halogen atoms has already been referred to (p. 59). The introduction of an atom of chlorine for hydrogen often raises the boiling-point some  $60^\circ$ , an atom of bromine about  $84^\circ$ , and an atom of iodine  $110^\circ$ ; and the introduction of a second or third chlorine atom further raises the boiling-point, but not to the same extent.

Extremely interesting is the fact that a saturated compound and its ethylene analogue have very nearly the same boiling-points (cf. propyl and allyl alcohols, both  $97^\circ$ ;  $C_7H_{16}$  and  $C_7H_{14}$ , both  $99^\circ$ ; propionic acid,  $140.7^\circ$ ; and acrylic acid,  $140^\circ$ ), although they differ considerably as regards most of their other physical characteristics. Further, methyl ketones, acetyl esters, and corresponding acid chlorides boil at very nearly the same temperature, e.g. acetone, methyl acetate, and acetyl chloride at  $55^\circ$ – $56^\circ$ ; propyl methyl ketone, methyl butyrate, and butyryl chloride at  $101^\circ$ – $105^\circ$  (*Schröder*, B., 1883, **16**, 1312).

## B. Melting-point

Although, on the whole, in any homologous series the melting-points of the solid members tend to rise with increase



in molecular complexity, in many series an alternating rise and fall is met with, the members containing an even number of carbon atoms melting at relatively higher temperatures than those with an odd number. This is the case with the higher fatty acids, as is readily seen when the melting-points are plotted against the number of carbon atoms. Many other series show a similar relationship, e.g. dibasic acids:

C<sub>4</sub>, 180°; C<sub>5</sub>, 97°; C<sub>6</sub>, 148°; C<sub>7</sub>, 103°; C<sub>8</sub>, 140°; C<sub>9</sub>, 106°; C<sub>10</sub>, 127°.

(Compare also *Beach*, Zeit. phys., 1904, 50, 43.) For amides, cf. J. C. S., 1908, 1033; 1919, 1210; 1927, 2926.

Another property which shows an exactly similar alternation is the heat of crystallization of the normal and oxalic series of acids (*Garner*, J. C. S., 1926, 2491). These effects are to be attributed to the manner in which the atoms are packed in the crystal. X-ray studies show that the long chains lie side by side in zigzag lines, with the result that the terminal group is situated on opposite sides of the zigzag in the even and odd numbers of the series (J. C. S., 1923, 3156; 1928, 3235), thus producing a difference in crystal packing. For summary cf. *Malkin*, Phys. Rev., 1930, 430; also Rec. Trav., 1933, 747. Mixed melting-point curves indicate the formation of a compound between two "even" acids but not between an "even" and an "odd" acid.

In the case of a group of closely related isomeric compounds it is found that the melting-point tends to rise with the number of side chains or branches, e.g. CH<sub>3</sub>·CH<sub>2</sub>·CH<sub>2</sub>·CH<sub>2</sub>·OH is a liquid, and C(CH<sub>3</sub>)<sub>3</sub>·OH melts at 25°; or again, glutaric acid melts at 97°, methyl-succinic at 112°, and dimethyl-malonic at 117°. The conversion of an acid into an ester always produces a lowering of the melting-point, and the methyl ester always has the highest melting-point of any of the alkyl esters derived from a given acid; in fact, in many cases the methyl esters are solids, and the ethyl and higher esters liquids at the ordinary temperature.

In the aromatic series the *p*-compound has a higher melting-point than the *o* and *m* isomerides. With a pair of isomerides the higher melting is always the more stable compound. *G. Schultz* (A., 1881, 207, 362) has shown that in the group of compounds,

Nitro → azoxy → azo ← hydrazo ← amine,

the melting-point increases up to the azo-compound, and then falls again to the amine. According to *Franchimont* (Rec., 1897, 16, 126), the melting-point of an organic compound is invariably raised when two hydrogen atoms attached to the same carbon are replaced by oxygen, or when a hydrogen atom is replaced by hydroxyl; cf.  $C_6H_5 \cdot CH_2 \cdot OH$  and  $C_6H_5 \cdot CO \cdot OH$ , or  $C_6H_6$  and  $C_6H_5 \cdot OH$ .

### C. Heats of Formation

The heat of formation,  $H_f$ , of a compound is defined as the number of calories liberated or absorbed when the gram-molecule of the compound is formed from its elements. In the case of carbon compounds this cannot be determined directly, and the usual method is to deduce it from the heat of combustion of the compound.

Thus for methane the heat liberated on burning 16 gm. of methane in oxygen is 212 kilo cal., whereas the heat liberated on burning 12 gm. of carbon and 4 gm. of hydrogen in oxygen is  $94 + 136 = 230$ . The difference  $230 - 212$ , i.e. 18, is the heat of formation of methane.\* It has recently been pointed out that the heat of formation of a compound should be expressed as the heat of formation of the gram-molecule from its component atoms; hence, in the above case, the heat required to convert 12 gm. of carbon and 4 gm. of hydrogen into atoms must be taken into account. This is usually termed *Heat of Atomization* and denoted by  $H_{At}$ . Hence if  $H_a$  is the heat of formation of the gram-molecule from its component atoms, then

$$H_a = H_{At} + P - Q,$$

where  $P$  is the heat of combustion of the elements, e.g. 12 gm. of carbon (graphite) and 4 gm. of hydrogen (as gas), and  $Q$  is the heat of combustion of the gram-molecule of the compound.  $H_a$  gives the total energy involved in the formation of all the links in the compound, and it will obviously be greater the smaller the value of  $Q$ , i.e. the stability of the molecule is greater the smaller the heat of combustion.

\* All the numbers in this section refer to kilo cal.

The values of  $H_A$  have, as a rule, to be obtained indirectly, e.g. from spectral observations; three common values are C 150, H 51.5, and N 104 kilogram cal. per gram-atom.

In the case of the heat of combustion of solids and liquids, e.g. naphthalene or *n*-pentane, the heats of fusion and of evaporation must be taken into account.

The earlier values for the heats of combustion indicated that in any homologous series there is a constant value for  $CH_2$  which is independent of the series examined, e.g. paraffins, olefines, alkyl chlorides, monohydric alcohols, &c., and is roughly 158.

This would indicate that the heat of formation is strictly additive, i.e. for a saturated hydrocarbon,

$$H_A = xA + yB,$$

where  $x$  and  $y$  are the number of C—C and C—H links, and A and B are the respective heats of formation of these links.

The method of obtaining the values for the links C—C and C—H can be illustrated by reference to methane and ethane both as gases.

*Methane.*  $Q = 212.7$ .

$$\begin{aligned} H_f &= -212.7 + 94.38 \times 1 + 34.19 \times 4 \\ &= +18.5. \end{aligned}$$

$$\begin{aligned} H_A &= 18.5 + 150 + 4 \times 51.5 \\ &= 374.5. \end{aligned}$$

This corresponds with 4 C—H links and hence the heat of formation of each C—H is 93.6.

*Ethane.*  $Q = 368.3$ .

$$\begin{aligned} H_f &= -368.3 + 2 \times 94.38 + 6 \times 34.19 \\ &= +25.6. \end{aligned}$$

$$\begin{aligned} H_A &= 25.6 + 2 \times 150 + 6 \times 51.5 \\ &= 634.6. \end{aligned}$$

This is due to 6 C—H links and 1 C—C link,

$\therefore$  Heat of formation of C—C is  $634.6 - 6 \times 93.6 = 73$ .

Other methods of obtaining values of the heats of rupture of C—H and C—C links are used, e.g. extrapolation of the infra-red band spectra or observations on predissociation give values agreeing fairly well with the above, but as a rule somewhat higher.

The values C—H and C—C differ according to the aliphatic or aromatic structure of the compound:

$$\begin{aligned} \text{C}_{\text{al}} - \text{H} &= 93.61, & \text{C}_{\text{ar}} - \text{H} &= 101.73, & \text{C}_{\text{al}} - \text{C}_{\text{al}} &= 71.14, \\ \text{C}_{\text{al}} - \text{C}_{\text{ar}} &= 79.4 & \text{and} & & \text{C}_{\text{ar}} - \text{C}_{\text{ar}} &= 97.17. \end{aligned}$$

The value for C=C in olefines is 123.2, and that for C≡C in acetylenes is 161.1, it being assumed that the values of C—H and C—C are the same in unsaturated as in saturated compounds.

For lists of heats of formation from atoms and of heats of formation of links cf. *Sidgwick*, "The Covalent Link", Chap. IV.

The more accurate determinations of *Rossini* (*Bur. Stand. J. Res.*, 1934, 735) show that in a given homologous series the value  $\text{CH}_2$  is not absolutely constant. The generalization holds good for saturated hydrocarbons with more than 5 carbon atoms. With the lower compounds the value  $\text{H}_2$  is greater than would be expected, and increases from *n*-butane to methane, which is 4.8 kg. cal. greater than the calculated value. For the saturated alcohols with less than 5 atoms the values are abnormal, but less than the calculated values, and with methyl alcohol the value is 4.2 less, even when corrected to zero pressure and zero temperature.

Cyclopropane and propylene give practically the same value indicating the great strain in the tri-ring.

**Heats of Hydrogenation.**—The hydrogenation of an olefine or a diene is usually an endothermic reaction, and the following values have been determined for different compounds in kg. cal. per mol.

Allene + $\text{H}_2$	- 41	1:3-Cyclohexadiene + $\text{H}_2$	- 26.7
Butadiene + $\text{H}_2$	- 26.7	Cyclo-pentadiene + $\text{H}_2$	- 22.2
1:4-Pentadiene + $\text{H}_2$	- 30.7	Benzene + $\text{H}_2$	+ 5.6
1:5-Hexadiene + $\text{H}_2$	- 36.4		

The results were obtained by determining the difference between the value for the ethylene and that for the corresponding diene, and in the case of benzene between 1:3-cyclohexadiene and benzene. The result with benzene shows the great resonance energy of benzene.

### D. Absorption Spectra \*

Absorption spectra—ultra-violet 185–400  $m\mu$ , visible 400–760  $m\mu$ , and infra-red 0.76–15  $\mu$ —have proved of value in the study of carbon compounds, and the results are usually depicted as graphs of the function  $\epsilon\lambda$ , where  $\epsilon$  is the molecular extinction coefficient and  $\lambda$  the wave-length. The absorption is proportional to the number of molecules in the light path, so that it depends upon the concentration and on the thickness of the layer. Thus

$$I = I_0 \times 10^{-\epsilon cd},$$

where  $I_0$  is the intensity of the incident light,  $I$  that of the emergent light,  $c$  is the molar concentration, and  $d$  is the thickness of the layer in centimetres.

In examining the spectra of a relatively transparent substance it is necessary to be absolutely sure of its purity, as a mere trace of a highly absorbing compound will completely change the absorption curve, e.g. 1 part of stilbene in 4000 of dibenzyl; on the other hand, even 1 per cent of a relatively transparent substance will have but little effect on a compound with marked absorption.

All saturated hydrocarbons, whether open-chain or cyclic, show little or no absorption. If a group introduced into one hydrocarbon produces characteristic absorption, then the same group introduced into any other saturated hydrocarbon will produce the same effect. The group is an absorbing group or **chromophore**. Of these there are four distinct classes:

- (a) Halogens or sulphur;
- (b)  $\cdot\text{NO}$ ,  $\cdot\text{NO}_2$ ,  $\cdot\text{NH}_2$ ;
- (c)  $\cdot\text{CN}$ ,  $\cdot\text{CO}_2\text{H}$ ,  $\cdot\text{C}_6\text{H}_5$ ,  $\cdot\text{C}_{10}\text{H}_7$ ;
- (d)  $>\text{C}:\text{O}$ ,  $>\text{C}:\text{S}$ ,  $\cdot\text{CH}:\text{CH}\cdot$ ,  $>\text{C}:\text{C}<$ ,  $\cdot\text{CH}:\text{N}\cdot$ ,  $\cdot\text{N}:\text{N}\cdot$ ;

and the most important of these are  $\text{C}_6\text{H}_5$ ,  $>\text{C}:\text{O}$ ,  $>\text{C}:\text{C}$ ,  $\cdot\text{CH}:\text{N}\cdot$ , and  $\cdot\text{N}:\text{N}\cdot$ .

The position of the absorbing group  $\text{X}$  in any homologous series does not appreciably affect the absorption, e.g. in the compounds  $\text{CH}_3(\text{CH}_2)_n\text{X}(\text{CH}_2)_m\text{CH}_3$  the absorption is inde-

\* *Lösungs Spektren*, H. Mohler, Jena, 1937. *Practical Aspects of Absorption Spectrophotometry*, R. A. Morton, Institute of Chemistry Lecture, 1938.



pendent of  $n$  and  $m$ . Even with compounds containing two absorbing groups  $X$  and  $X'$ , e.g.  $RX(CH_2)_nX'R$ , the absorption is practically independent of  $n$ , the only effect being a slight rise in  $\epsilon_{\max}$  with  $n$ . Thus succinic and glutaric acids give the same absorption, and also diphenoxymethane and diphenoxydecane.

One of the most marked effects is seen in conjugated polyenes. In the simple olefine the absorption is in the extreme ultraviolet region ( $<185 m\mu$ ), but becomes displaced in the direction of longer wave-length on conjugation, and compounds with several conjugated double bonds are yellow or orange and those with 12 or 15 purple- or green-black (cf. *Kuhn*, Diphenyl polyenes, J. C. S., 1938, 605). For isoprene  $\lambda = 220$ , cyclopentadiene 238, sorbic acid 261, and octatrienoic acid 303,  $Ph(CH:CH)_5Ph$  433, and  $Ph(CH:CH)_{15}Ph$  570. There is also an increase in the intensity of the absorption with an increase in the number of conjugated double bonds. Several double bonds not conjugated do not appreciably affect the absorption.

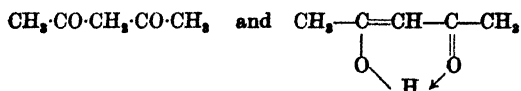
The increase in  $\lambda$  becomes smaller for each additional conjugated double bond, but the intensity of the absorption increases regularly with the number of such bonds.

In ketones and azo-compounds containing the chromophores  $>C:O$  and  $-N:N-$  the value of  $\lambda_{\max}$  increases with the complexity of the alkyl groups attached to the chromophores, e.g. from 279 for acetone to 375 for *s*-isopropylacetone, and 345 for benzophenone; the corresponding values for  $\epsilon_{\max}$  are 15, 82, and 112, i.e. comparatively small.

With an  $\alpha\beta$ -unsaturated ketone, i.e.  $C:O$  and  $C:C$  conjugated there are two distinct bands, e.g. mesityl oxide,  $CH_3 \cdot CO \cdot CH:C(CH_3)_2$  has  $\lambda_{\max}$  229.5 and 327 in *n*-hexane solution, but varies with the solvent in passing from hexane to methyl alcohol and water; the first band increases whereas the second decreases. The two bands can be regarded as due to the  $C:C$  and  $C:O$  linkings respectively as modified by conjugation.

The ketones and azo-compounds have, in addition, a band of high intensity, e.g. acetone with  $\lambda_{\max}$  190  $m\mu$  and  $\epsilon_{\max}$  about 10,000, and methylazobenzene with 258 and 4000 respectively. It has been suggested that the two bands for acetone may be due to the two forms:  $\lambda$  190 to  $Me_2C:O$  and  $\lambda$  280 to  $Me_2C \diagdown O-$ .

Enolization does not affect the wave-length but increases the intensity, thus both



have  $\lambda_{\max}$  275  $m\mu$ , but the former has a low value for  $\epsilon_{\max}$  and the latter a high value.

Benzene, both liquid and vapour, shows a group of 8 narrow maxima in the region 229–270  $m\mu$ , and a second group near 190–210  $m\mu$ ; the former group has low and the latter high intensity. Condensed benzene rings show marked change; the longest wave-length in benzene is 269, in naphthalene 311, and in anthracene 476  $m\mu$ , with corresponding values of  $\epsilon_{\max}$  39, 280, and 9700.

Methyl, ethyl, allyl and chlorine substituents in the benzene ring have very little effect on the wave-length or intensity of the absorption, whereas OH, OMe, OEt, CN, CO<sub>2</sub>H, CO<sub>2</sub>Et, NH<sub>2</sub>, displace  $\lambda_{\max}$  appreciably and produce a tenfold increase in  $\epsilon_{\max}$ , indicating an increased tendency for electronic transitions. The greatest effect is produced by  $\cdot\text{CO}$  in the form of an aldehyde or ketone, and a  $\cdot\text{C}:\text{C}$  as in propenylbenzene, cinnamyl alcohol and isoeugenol, where  $\lambda_{\max}$  has the values 309–320 owing to the conjugation of the  $\cdot\text{C}:\text{C}$  with the benzene ring.

The presence of several olefine linkings produces but little effect unless they are conjugated. The effect of conjugation is seen in the following table:

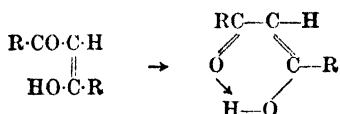
	$\lambda_{\max}$	$\epsilon_{\max}$
CHPh:CHMe .. ..	246 *	10,000
CHPh:CH:CH <sub>2</sub> .. ..	282	> 10,000
CHPh:CH:CO:CH <sub>2</sub> .. ..	285	23,000
CHPh:C(OH):CO:CH <sub>2</sub> .. ..	310	20,000
C <sub>6</sub> H <sub>5</sub> :CO:CHMe:CO:CH <sub>2</sub> .. ..	247 †	11,600

Certain *cis* and *trans* stereoisomerides, such as the two stilbenes and the two cinnamic acids, show certain differences; in both these cases the band 280  $m\mu$  is about twice as intense for the *cis* compound as for the *trans* compound.

\* In addition bands at 278 and 279 with  $\epsilon$  500.

† In addition bands at 284 and 310 with  $\epsilon$  1500 and 200 respectively.

When a compound of the type  $C_6H_5 \cdot CO \cdot CHMe \cdot CO \cdot CH_3$  enolizes there is always the possibility of the formation of stereo-isomeric enols, but the proportions of the two stereo-isomerides do not appear to vary with the solvent, e.g. hexane, alcohol or water, probably owing to the one enol being fixed by means of a hydrogen bond:



In the case of ethyl benzoylacetate in different solvents the percentage of enol can be determined by the bromine method (Chap. LIII, A.) and from the observed values of  $\epsilon_{\max}$ , the value for  $\lambda_{\max}$  being the same, the values for the true keto and enol forms can be calculated.

	$\lambda = 242$	$\lambda = 285$
$C_6H_5 \cdot CO \cdot CH_2 \cdot CO_2Et$	$\epsilon_{\max} = 10,600$	1200
$C_6H_5 \cdot C(OH) : CH \cdot CO_2Et$	$\epsilon_{\max} = 6,000$	13,000

Absorption spectra have proved of value in various ways in the study of carbon compounds.

(1) *Hartley* and *Dobbie* used the absorption method for determining the structures of certain tautomeric substances of the lactam-lactim type, e.g. isatin. By comparing the absorption bands of isatin and its two methyl ethers I and II,



it was shown that the bands of isatin resemble those of the pseudo methyl ether II. As the structure of the two ethers can be established from their reactions, it follows that isatin

has the lactam structure  $C_6H_4 \begin{array}{c} \diagup NH \\ \diagdown CO \end{array} CO$ . A similar method

applied to carbostyryl (Chap. XLIV, A2) indicates that it also has a lactam structure  $C_6H_4 \begin{array}{c} \diagup CH : CH \\ \diagdown NH \cdot CO \end{array}$  (J. C. S., 1899,

640). The method has been applied to the study of certain alkaloids (*ibid.* 1911, 1340; 1914, 1639).

(2) The method is of value for determining small amounts of strongly absorbing compounds in a relatively transparent substance, e.g. benzene in *cyclohexane*, carbon disulphide in carbon tetrachloride, and dehydrocholesterol in cholesterol. It is also used for the determination of small amounts of copper and lead in carbon tetrachloride solutions containing diphenylthiocarbazone (dithiazone D),  $\text{NHPH}\cdot\text{NH}\cdot\text{CS}\cdot\text{N}:\text{NPh}$ .

The determination of  $p_{\text{H}}$  of certain dye solutions can be determined. With many indicators different concentrations of acid give practically the same bands but with very different intensities, and as for many the  $\epsilon_{\text{max}}$  is a function of  $p_{\text{H}}$ , this affords a method for determining the latter.

The method has proved of value in examining many biochemical products, e.g. in estimating the concentration of vitamin A in certain materials, for establishing relationships of irradiated ergosterol products and for elucidating the structure of porphyrins. Thus alkyl groups in any of the positions 1-8 in the porphyrin molecule (Chap. LXIV, D.) produce only slight effects on the absorption, whereas  $\cdot\text{CO}\cdot\text{CH}_3$  and  $\cdot\text{CO}_2\text{Me}$  produce a distinct effect. Alkyl substituents in positions  $\alpha$ - $\delta$  produce a third type of absorption.

**Infra-red Absorption.**—Bands are also obtained in the infra-red spectrum, but these have not been studied to the same extent as ultra-violet bands. Relatively few solvents are available, namely,  $\text{CCl}_4$  and halogenated methanes and ethanes, and interesting observations have been made with phenols. Most of these show a marked maximum at  $8.75\ \mu$ , but this is not found in phenols where hydrogen bond chelation is possible, e.g. *o*-hydroxybenzaldehyde. An examination of solutions of phenols of different concentrations shows the disappearance of a band ( $2.95\ \mu$ ) as dilution increases, and this may be a band due to association of phenol molecules.

## E. The Raman Effect \*

When a strong beam of monochromatic light of known frequency is passed through a transparent medium a scattering of the rays takes place, and the scattered light when

\* For reviews, cf. Rep., 1934, 21, and *Hibben*, Chem. Rev., 1936, 1; also *Kohlrausch*, Der Smekal-Raman Effekt (Berlin, 1938); *Hibben*, The Raman Effect and its Chemical Applications, New York, 1939.

resolved has, in addition to the original radiation, a series of lines lying on both sides of this and termed *Raman* lines. Each substance has a specific scattering effect; this is usually small, but may be studied with the aid of a spectrometer with photographic attachment (*Kohlrausch*, 1931). This displacement of frequency was predicted by *Smekal* in 1923 but first observed by *Raman* in 1928, and is usually termed the *Raman* effect.<sup>1</sup> It is extremely general and occurs with all phases of matter under very varying conditions. Up to 1936 about 1370 organic compounds had been studied by this method. The differences of energies corresponding with the separation of the lines from that of the incident beam agrees with the energies of the infra-red spectrum of the same medium, and hence *Raman* spectra are of value in the study of the latter as they are much more readily observed. If  $\nu_0$  is the frequency of the original beam, then  $\nu_0 - \nu'$ , the *Raman* frequency, is independent of  $\nu_0$  but depends only on the nature of the molecules constituting the medium.<sup>1</sup>

The use of the *Raman* effect has advantages over certain other physical methods. Each molecule has its own *Raman* effect, and the presence of a second compound has no effect on this provided chemical reaction, e.g. addition, does not occur between the two. Again, the molecular effect is made up of the individual effects of the different links in the molecule, and on the whole each of these is not appreciably affected by the presence of other links. For a given spectrum the intensity of the effect is directly proportional to the number of scattering molecules present, and for constant volume is proportional to the concentration.

It follows that a study of *Raman* frequencies is of value in the identification of individual compounds, and also in detecting and even estimating impurities in a given compound. It is particularly useful in detecting the presence of small amounts of unsaturated compounds in a saturated, e.g. 2 per cent of propylene can be detected in cyclopropane or 0.4 per cent of cinnamene in ethylbenzene; also for estimating benzene and toluene in mixtures, and in the study of mixtures of terpenes.

*Raman* spectra have proved of value in detecting replacement of hydrogen by deuterium. The compounds  $C_2H_2$ ,  $C_2HD$ , and  $C_2D_2$  have distinct spectra. When the dry gases  $C_2H_2$  and  $C_2D_2$  are mixed no lines characteristic of  $C_2HD$  can

be observed, but a trace of water produces the  $C_2HD$  lines, indicating that exchange of H and D between the two compounds occurs only in the presence of moisture.

The Raman effect has also proved of value in studying the degree of electrolytic dissociation of compounds, the study of *cis* and *trans* isomerism, esterification, hydrolysis, keto-enolic tautomerism, polymerization, and the formation of additive compounds.

The method has also been used for calculating (a) the strength of the link between two atoms; (b) the frequency and amplitude of atomic vibrations; in certain cases for determining the spatial configuration and anisotropy of a molecule, and from these data specific heats, relative heats of dissociation, and heats of fusion of organic compounds.

Raman frequencies fall into four main groups:

1. Greater than 2800.\* Characteristic of group containing the light H atom.
2. Between 2400 and 1900. Characteristic of compounds with a triple bond.
3. Between 1800 and 1300. Characteristic of compounds with a double link.
4. Below 1000. Characteristic of single links with the exception of X—H link.

For a compound containing several of these types of links,

e.g.  $\begin{array}{c} \text{H} \\ \diagup \\ \text{C} : \text{CH} \cdot \text{CH} : \text{O} \\ \diagdown \\ \text{H} \end{array}$ , all three types 1, 3, and 4 will be represented in the spectrum, and the one type has only a slight effect on the other types. /

The values for common links met with in organic compounds are: C—H 2930 in aliphatic and 3050 in aromatic compounds, C—C varying from 997 to 1590, C—O 820–880, C—N 910–930, C=C 1600 in aliphatic and 1590 in benzene, C=O varying from 1640 to 1730, C:N about 2150, N=O 1565, C≡C 1960, C≡N 2245, C—Cl 710, C—Br 600, and C—I 530.

The value found for carbon monoxide, 2155, agrees with the type C≡O, i.e.  $C \rightleftharpoons O$ , and the value for isonitriles, namely 2146–2161, with  $-N \rightleftharpoons C$ .

Organic nitro compounds give a value 1400, and approximately the same value is given by concentrated nitric acid

\* All these numbers are  $\text{cm}^{-1}$ , and for simplicity  $^{-1}\text{cm}$ . is omitted.

and sodium nitrite; hence all three contain the  $\text{—N} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{O} \end{array}$

group. Sodium nitrate gives a different value, 1046, and as nitric acid is diluted the nitro-group value disappears and is replaced by the 1046 value characteristic of the nitrate ion.

Among the aliphatic hydrocarbons the *Raman* spectrum of methane is comparatively simple; the main effect is the *Raman* frequency C—H 2918, but other minor shifts can be observed. In ethane there are two marked shifts, namely C—H 2900 and 2955 and C—C 993. As the complexity of the molecule increases, the main shifts for C—H and C—C persist with slight alterations, e.g. C—C 867 in propane and 834 in butane, but additional shifts make their appearance, e.g. 800–1100 and others comparatively small between 200 and 700. In the case of isomeric hydrocarbons there are appreciable differences between the isomers.

In benzene homologues two shifts due to C—H are observable: one the aliphatic value, and also a value of 3050 probably due to the =C—H group, as a similar value is met with in allyl compounds.

The *Raman* spectra for olefine compounds, whether open chain or cyclic, show a shift of from 1600 to 1650, which is quite different from any lines due to any other type of oscillation. The lines are very clear and are of great value in determining the presence of such linkings in compounds, and have proved of value in determining the structure of terpenes.

The attachment of an alkyl group to one of the two C atoms, C:C, has an effect different from that of OH or halogen, and a  $\beta$ -substituent, i.e.  $\beta$  to olefine link, has a smaller effect than an  $\alpha$ -substituent. In the case of *cis* and *trans* isomerides the *cis* compound has always the lower value, by some 16 to 20 units, and the presence of a small amount of a *cis* compound in the *trans* can easily be detected. For conjugate ethylene links the value is about 1644, but in allenes it is only 1100.

The carbonyl group produces a shift varying from 1645 to 1800, depending on the structure of the compound. It is least in acids, namely 1654, approximating to the olefine value, and varies within narrow limits when alkyl groups are introduced, e.g. di- and tri-methyl-acetic acids. For methyl and ethyl esters the value is about 1730, for acyl chlorides 1790, for ketones 1705, and for aldehydes 1718. The introduction

of chlorine in all these compounds tends to raise the value of the shift, e.g. to 1768 for methyl trichloroacetate. In unsaturated carbonyl compounds the conjugation of C:C with C:O produces a diminution of the carbonyl shift by some 40 units, and in  $\alpha\beta$ -unsaturated acids it appears that the carbonyl shift is weakened almost to extinction.

It is clear that the marked effect of an olefine link can be utilized for detecting the presence of enols in keto-enolic tautomerides. The characteristic shift is observed with acetoacetic esters and their mono-alkyl derivatives, but not with dialkyl derivatives, where the formation of an enol is impossible.

The acetylene link produces a shift of 2100 to 2250 units. Acetylene has 1975, methylacetylene 2123, and dimethylacetylene 2234, with a second shift which is characteristic of all disubstituted acetylenes.

The cycloparaffins give characteristic shifts, e.g. cyclopropane and its derivatives about 1200, and the substituted derivatives a second shift which varies with the number of carbon atoms in the molecule.

Other rings have different values, and the effects of substituents and of olefine links have been studied.

The introduction of substituents into the naphthalene molecule produces a marked effect on the *Raman* spectrum and varies according to the  $\alpha$  or  $\beta$  position of the substituent.

The bicyclic compounds  $\alpha$ -thujene,  $\Delta^3$ -carene,  $\Delta^4$ -carene, sabinene, and pinene all give a similar type of spectrum.

From the *Raman* spectra it has been found possible to determine the strengths of the commoner links in carbon compounds. The value calculated is termed the restoring force per unit displacement and is denoted by  $f$ . The relationship for a marked displacement characteristic of any particular link is given by  $v = \frac{1}{2\pi} \sqrt{f/\mu}$ , where  $v$  is the *Raman* shift dynes/cm. and  $\mu$  is the "reduced mass".

Values have been calculated for  $f \times a/2$ , termed the average value of restoring force,  $a$  being the amplitude of the vibration. The following are the numerical values of  $f \times a/2$  in dynes  $\times 10^4$ . For X—X (where X is C or O) the value is of the order 2.1, and for X=X (where X is C, O, or N) 4.3, for X $\equiv$ X 6.4, i.e. roughly of the order 1 : 2 : 3, and is independent of the type of link, i.e. C:O or C:N.



The values for X—H range from 4.55 for H—H to 2.52 for H—I. For C—X (where X is an element other than H) the value ranges from 2.25 for C—O to 1.05 for C—I.

The values of the mean restoring forces may be regarded as a measure of the work necessary to sever the bond involved in any particular link, and should therefore be proportional to the heat of dissociation of the bond, and this has been proved to be roughly correct.

Thus the heat of dissociation of X—X varies from 50 to 70 kilo calories, X=X from 125 to 160, and X≡X from 165 to 235.

The study of polarizability by *Placzek* (1931) has given interesting results bearing upon the symmetry of molecules, and the results have confirmed in most cases the structures arrived at by other methods.

## F. X-ray Examination \*

The usual method adopted is due to *Bragg*, and is based on the principle of using a crystal surface as a grating for X-rays. The rays penetrate to a minute depth, and thus encounter an ordered array of atoms in planes which make up the crystal lattice. Each atom acts as a diffraction centre sending out wavelets. In certain directions these will be in step and will combine to form a beam ("reflected" beam). With wavelets in other directions the crests of one will coincide with the troughs of the following, and no "reflected" beam will be observed. Observations are made from the different types of faces. *Bragg's* equation  $n\lambda = 2d \sin \theta$  expresses the relationship between  $d$ , the distance between reflecting planes,  $\lambda$  the wave-length of the X-ray employed, and  $\theta$  the angle of reflection. If  $\lambda$  and  $\theta$  are known, then  $d$  is readily calculated.

When distinct crystals cannot be obtained a fine powder may be used (*Debye, Scherrer, Hull*). Certain grains will reflect from one crystal plane and others from another, the result, when a beam of X-rays is passed through such a powder and then allowed to impinge normally on a photographic plate, being a central spot surrounded by a series of uniform rings,

\* For brief summary, cf. *Emeleus and Miall*, *J. Ind.*, 1936, 638; cf. also *Rep.*, 1933, 411, and 1935, 227; *Applied X-Rays*, *G. L. Clark*, New York, 1940.

and each ring corresponds with one set of planes of the crystalline material.

The atoms in a crystalline material have an ordered arrangement in space, termed a *space lattice*, and this orderly pattern repeats itself throughout the body of the crystal. The smallest unit volume of the crystal which exhibits this pattern is the unit *cell*, which possesses the same symmetry as the macro cell, which is built up of these units. One of the functions of X-ray analysis is the determination of the size of these unit cells and the number of atoms or molecules or ions they contain. The size is usually of the order of 10A for the side, and the number of molecules in the cell less than five.

Each year sees the publication of an enormous amount of work on X-ray analysis, and only a summary of some of the more important results can be given. *Bernal and Crowfoot* (Rep., 1933, 411) summarize the various stages in the examination as follows:

1. X-ray photographs of the crystal. Of great value in proving the identity of two crystalline compounds.

2. Determination of cell size. This combined with an accurate determination of the density of the crystal gives the most accurate method for determining the absolute molecular weight, which is usually a simple multiple of the true molecular weight.

3. Determination of space group and molecular symmetry by a combination of the study of X-ray photographs with a determination of polarity. This gives a maximum molecular size and serves to differentiate between pure substances and molecular compounds as in the case of quinhedrone. It also gives a value for the minimum symmetry which is of value in stereochemical studies.

4. Determination of general arrangement of the molecules in the cell. The X-ray evidence combined with knowledge of optical or magnetic anisotropy often gives indications as to the disposition of molecules in the crystal and hence of their size and shape. In organic compounds where intermolecular forces are weak the molecule behaves in the crystal very much as in a gas, and the anisotropy of the crystal is a product of that of the individual molecules and of their mutual orientations. Long molecules have positive anisotropy, flat molecules negative, and round ones quasi anisotropy. This has

proved of value in discussions relating to the structure of vitamins B1 and C, and also in many membered rings,  $C_nH_{2n}$ , where  $n = 12-30$ , which structure resembles the  $n$ -paraffins, the ring being drawn out into a double chain with small rings at each end. The cross-section of the ring is 37.5 Å, practically double that of the paraffin chain, 18.3 Å. Difficulties arise when intermolecular forces are large, as in polyalcohols, sugars, and many acids.

5. Determination of atomic positions. When the positions of molecules in a crystal are known, the exact positions of the atoms can be found by a laborious process of trial and error, so as to give good agreement between observed and calculated intensities of reflection.

6. Determination of electronic densities (*Fourier analysis*), and from these, interatomic distances and valency angles.

Stages 5 and 6 involve refined measurements of intensity and laborious computations involving many weeks of time, and hence *complete* analyses of organic crystals are rare. Compounds so examined include aromatic hydrocarbons both mono- and polycyclic, urea, thiourea, hexamethyltetramine, benzoquinone, *p*-dinitrobenzene, and cyanuric triazide, and to a certain extent pyranose sugars, and from these the following interatomic distances Å for the different links have been obtained: C—N 1.42–1.37, C=O 1.25, C—S 1.64, C—C (arom.) 1.41, C—C (aliph.) 1.47, C—C (between two benzene rings) 1.48 (cf. Table, p. 1284).

*Pauling and Huggins* (Z. Kryst., 1934, **87**, 205) give the following values for atomic radii and these can be used for calculating interatomic distances in co-valent bonds: H 0.29, C 0.77, N 0.70, O 0.66, F 0.64, Cl 0.99, Br 1.14, I 1.33, S 1.04. Double bond, C 0.69, N 0.63, O 0.59, S 0.94. Triple bond, C 0.61, N 0.55.

Some of the more important conclusions drawn are:

1. All aromatic compounds, whether single ring or condensed rings, have a planar structure. These flat molecules tend to pack more and more into parallel sheets resembling the structure of graphite as the number of carbon atoms increases.

2. In cyclohexane the atoms appear to lie in a single plane, and in dibenzyl,  $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot C_6H_5$ , the two benzene rings lie in parallel planes, and the distance between a ring C atom and a chain C atom is 1.47 Å, and between the two C atoms of the chain 1.58 Å.

3. In benzoquinone the values are C—C (both ring) 1.50, C=C (both ring) 1.32, and C=O 1.14, with an angle of  $109^\circ$  between C—C—C and  $125^\circ$  between C=C—C.

4. The molecules  $\text{CH}_4$  and  $\text{Cl}_4$  form a cubic lattice with regular tetrahedra. In urea the central carbon atom is enclosed in a triangle with one O and two N's at its corners: C—N = 1.37, and C=O = 1.25 Å. In thiourea the C is at the apex of a tetrahedron with S, N, and N at the other three corners: C—N = 1.35, C=S = 1.64.

5. With the sugars the examination is complicated by the interaction of the hydroxyl groups and the linking together of molecules in all directions in the lattice. With completely methylated sugars such interplay does not occur, and they all have much the same thickness, 4.20–4.69 Å, and probably have what is termed the flat type of ring, namely 5 carbon atoms in one plane and the oxygen of the ring slightly above this plane (J. C. S., 1935, 978, 1495).

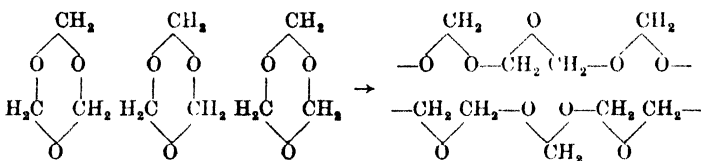
6. A comparison of the orthorhombic crystals and film X-ray examination of the paraffin hydrocarbon  $\text{C}_{29}\text{H}_{60}$  shows that the film has a dimension of 38.6 Å, and the crystal cells all a length of 77.2 about the *c* axis, indicating that the cell has two molecules arranged lengthwise along the *c* axis. The distances between adjacent and alternate carbon atoms are 1.54 and 2.54 Å with a zigzag arrangement of the C atoms. The angle is  $109^\circ 28'$ , and there is a break of 3.09 Å between the two molecules, and between the C atoms of one chain and the C atoms of a parallel chain a distance of 3.7–4.0 Å. A comparison of homologues indicates an increase in length of 1.27 for each  $\text{CH}_2$ .

With monobasic acids the spacing is roughly twice that of the corresponding paraffin, and it is concluded that the film is 2 molecules thick, consisting of 2 molecules end on with their carboxyl groups in the middle. With dibasic acids the film is only 1 molecule thick.

7. Fibres, &c. X-ray examination has been applied to proteins, polysaccharoses, and rubber (*Astbury*, *Fundamentals of Fibre Structure*, 1933).

8. Trioxymethylene crystallizes in the hexagonal system with 6-membered ring molecules arranged in order along the hexad axis. On exposure to light the presence of formaldehyde nuclei appears in the crystals, and, starting from these nuclei, fibrous polyoxymethylene molecules appear, the fibre axis lying along

the hexagonal axis, and it is probable that the ring polymeride is transformed into a chain polymeride.



In the case of cellulose a unit of 10.3 Å occurs—this is the length of an anhydrous  $\beta$ -glucose unit—and these units form a chain-like polymer (Chap. LVI, D.). In the unit cell the chains are parallel, and the result is that of a monoclinic cell with the axis lengths  $a = 8.3$ ,  $b = 10.3$ , and  $c = 7.9$ , and  $\beta = 84^\circ$ .

9. In resorcinol there is a distance of 1.39 Å between the carbon atoms, and the C—C links of the ring have an angle of  $120^\circ$ . The C—O distance is 1.36 Å, and the angle between the C—O link and the extended C—C link is  $58.5^\circ$  (Robertson, P. R. S., 1936, A., 157, 79). The molecules have a spiral packing in the crystal so that the OH groups are brought within a distance of 2.66–2.74 Å of one another, so that hydroxyl bond formation can occur without bringing the C atoms nearer than 3.5 Å.

10. A careful examination of *p*-dinitrobenzene has been made by James, King, and Horrocks (*ibid.* 1935, A., 153, 225). The molecule as a whole has a centre of symmetry; the nitro group itself is nearly but not quite planar and is nearly coplanar with the benzene ring, one oxygen being in this plane and one slightly above. The interatomic distances and angles have all been determined, and the nitro group has produced an appreciable effect on both. The compound has no dipole moment, and hence the two oxygens in the nitro group may be equivalent and no co-ordinate link present.

11. Cyanuric triazide (Knaggs, *ibid.* 1935, 150, 576) has a planar structure with a ring of alternating N—C atoms, but the ring is not a regular hexagon but has alternate angles of  $113^\circ$  and  $129^\circ$ . The azide groups are linear and attached to the C atoms of the ring. The structure may be a resonance formula between  $-\text{N}=\text{N}=\text{N}$  and  $-\text{N}\leftarrow\text{N}\equiv\text{N}$ .

12. *Carboxylic acids*.—This group has been studied in oxalic acid and the oxalates. The oxalate group has a

planar configuration with a centre of symmetry. Cf. also *Robertson* (J. C. S., 1936, 1817), who points out distinct differences between values for oxalic acid dihydrate and the oxalate ion.

The diffraction of X-rays by amorphous solids, gases, and vapours has also been studied.\* The X-ray by passing through a gas becomes scattered, and this effect can be registered on a photographic film which records at the same time the position of the original ray. The film gives a fixed spot surrounded by a small number of diffuse concentric rings with a series of maxima and minima, the intensity of the rings decreasing with the distance from the central spot. The intensities can be plotted by means of a photometer curve with scattering intensity as ordinates and the angle of scattering as abscissæ. These curves can then be utilized for calculating atomic distances. When this method is applied to the vapours of  $\text{CCl}_4$ ,  $\text{CHCl}_3$ , and  $\text{CH}_2\text{Cl}_2$ , where the scattering is mainly due to the presence of the Cl atoms with a number of planetary electrons, it is found that the distances between the Cl atoms in the three compounds are respectively 2.98, 3.10, and 3.20 Å. Also with the *cis* and *trans*  $\text{CHCl:CHCl}$  the distances between the two Cl atoms are respectively 3.7 and 4.7 Å. In 1:2-dichloroethane the distance is 4.4, indicating that the mean position of the two Cl atoms corresponds roughly to that of the chlorine atom in *trans* dichlorethylene.

For the study of phthalocyanines (Chap. LIX, L.), see *Robertson* (J. C. S., 1936, 1195), and for other organic compounds, *Rep.*, 1936, 218; 1938, 194.

**Electron diffraction** has been studied in much the same manner but with different apparatus, and the values of the lengths of certain links thus determined agree with those given by X-ray measurements. This method gives the following values for distance between iodine atoms in diiodo-benzenes: *ortho* 4.0, *meta* 5.97, and *para* 6.85 Å.

\* *Randall*, The Diffraction of X-rays and Electrons by Amorphous Solids, Liquids and Gases, 1938.

## G. Dipole Moments \*

If the centres of action of the positive and negative parts of a molecule, termed by *Lowry* the electric centroids, do not coincide the molecule is polar. It is electrically equivalent to a rod with a + charge at one end and a - charge at the other, and in an electric field it tends to arrange itself with the - end towards the + pole of the field. Every *isolated* atom is non-polar, and, as a rule, with a covalent bond where the electrons are shared equally between two atoms the molecule is non-polar, e.g.  $H_2$ ,  $N_2$ , but if they are shared unequally the molecule becomes polar, and the great majority of compounds with covalent links are of this type, e.g.  $CH_3Cl$ ,  $C_2H_5\cdot OH$ ,  $C_6H_5\cdot NH_2$ .

Compounds with symmetrical formulæ, e.g.  $CH_4$ ,  $C_2H_6$ ,  $C_6H_6$ ,  $C_{10}H_8$ ,  $C_6H_{12}$ , are non-polar.

The dipole moment is expressed by the product of one of the charges and the distance between them.

For an electrovalent link, e.g.  $NaCl$  the dipole moment is the product of the charge on a univalent ion, i.e.  $4.77 \times 10^{-10}$  electrostatic units, and  $2.81 \times 10^{-8}$  cm., i.e.  $13.4 \times 10^{-18}$  units, usually termed debyes.

The methods of measuring dipole moments are based upon (1) the determination of the dielectric constant. This gives the most accurate determination; (2) the optical method due to *Debye* and *Lange*, which is less accurate; (3) molecular beam method (*Fraser*, *Molecular Rays*, Cambridge, 1931). This method is still less accurate and is used only when methods 1 and 2 are not available, e.g. with relatively non-volatile or insoluble compounds. Methods 1 and 2 give best results with determinations made in the gaseous phase or in very dilute solution in non-polar solvents.

The following deductions have been drawn from measurements made by the above methods.

\* *R. J. W. Le Fèvre*, *Dipole Moments*, London, 1938. *P. Debye*, *Polar Moments*, 1929. *C. P. Smyth*, *Dielectric Constants and Molecular Structure*, 1931. For summaries, (a) *Sidgwick*, *The Covalent Link in Chemistry*, 1933, Chap. V; (b) *Waters*, *Physical Aspects of Organic Chemistry*, 1935, Chap. IV; (c) *Emeleus and Miall*, *J. Ind.*, 1937, 33; (d) *Trans. Far.*, 1934, and appendix.

**Non-polar Molecules.**—The great majority of diatomic molecules  $X_2$ , i.e. both atoms the same, are non-polar, with the exception of  $Cl_2$  and  $Br_2$ . Triatomic molecules of the type  $B \cdot A \cdot B$  are non-polar when the three almost lie in a straight line, e.g.  $HgCl_2$ ,  $CO_2$ ,  $CS_2$ . If, however, the links form angles the compound is polar.  $SO_2$  is probably  $O=S \rightarrow O$ . The tetra-atomic molecules  $NH_3$ ,  $PH_3$ , and their alkyl derivatives are all polar and have the tetrahedral structure. Compounds of the type  $AB_4$  should be non-polar with planar or tetrahedral configurations. Most paraffins are non-polar, the introduction of  $CH_3$  for  $H$  producing no polar effect.

The methods described give the moment of the whole molecule, but this is the sum of a series of partial moments characteristic of each type of link in the molecule. Each of these is a *directional* moment and the molecular moment is the vector sum of these individual moments. If the value of each partial moment were known it would be possible to calculate the molecular moment of any compound.

**Moments of individual Links and Direction of Moments.**—The fact that the molecule of a hydrocarbon is non-polar does not necessarily mean that each link  $C-H$  or  $C-C$  is non-polar, as no matter what the dipole moments of the  $C-H$  link in methane were, the symmetrical spatial structure of the molecule would render this non-polar. For any given covalent link  $A-B$  it is necessary to know the direction of the moment, i.e. which atom is  $+$  and which  $-$  charged. The method of depicting a dipole is by placing an arrow pointing away from the  $+$  end and crossed at the  $+$  end, e.g.  $\overset{+}{\text{C}} \overset{\rightarrow}{\text{---}} \text{Br}$ . The method of determining the direction was suggested by *J. J. Thomson* with a para-disubstituted derivative of benzene,  $C_6H_4X_2$ ; the structure is planar and the two links  $C-X$  lie in a straight line, and their polarities neutralize one another, so that the molecule is non-polar. With a para compound  $C_6H_4XY$ , when the  $C$  atom is  $+$  in both links, i.e.  $\overset{+}{\text{C}} \overset{\rightarrow}{\text{---}} \text{X}$  and  $\overset{+}{\text{C}} \overset{\rightarrow}{\text{---}} \text{Y}$ , the dipole of the compound will be the difference between the dipole moments of the compounds  $C_6H_5X$  and  $C_6H_5Y$ ; whereas with  $\overset{+}{\text{C}} \overset{\rightarrow}{\text{---}} \text{X}$  and  $\overset{+}{\text{C}} \overset{\leftarrow}{\text{---}} \text{Y}$  the dipole of  $C_6H_4XY$  will be the sum of the two dipoles, i.e. will be greater than the moment of either  $C_6H_5X$  or  $C_6H_5Y$ . It is assumed that in nitrobenzene the direction is



C—NO<sub>2</sub>, i.e. away from the ring. Then by comparing the dipole moments of the following compounds:

Nitrobenzene	..	..	3.9	<i>p</i> -Nitrochlorobenzene	2.6
Chlorobenzene	..	..	1.55		
Nitrobenzene	..	..	3.9	<i>p</i> -Nitrotoluene	4.5
Toluene	..	..	0.4		
Nitrobenzene	..	..	3.9	<i>p</i> -Nitraniline	7.1
Aniline	..	..	1.6		

the following conclusions can be drawn:

$\overset{+}{\text{C}}-\overset{-}{\text{Cl}}$ ,  $\overset{+}{\text{C}}-\overset{-}{\text{CH}_3}$ ,  $\overset{+}{\text{C}}-\overset{-}{\text{NH}_2}$ , and by similar methods  $\overset{+}{\text{C}}-\overset{-}{\text{CN}}$ .

The table below gives a list of the usually accepted values for the dipole moments of the commoner links in organic compounds expressed in the usual units but omitting X10<sup>-18</sup>. These values have been calculated by methods in-

TABLE

Link	Moment	<i>d</i> in Å	Fraction of Electronic Charge	Bond Refractivity
H—C	0.2	1.14	0.04	1.7
H—N	1.5	1.08	0.25	1.8
H—P	0.55	1.24	0.1	
H—O	1.6	1.07	0.31	1.85
H—S	0.8	1.43	0.6	
C—N	0.4	1.48	0.06	1.55
C≡N	3.3	1.15	0.61	
C—O*	0.9	1.47	0.13	1.43
C=O*	2.5	1.27	0.42	3.42
C—S	1.2	1.83	0.15	
C=S	3.0	1.59	0.40	
C—F	1.5	1.45	0.22	1.6
C—Cl	1.7	1.74	0.21	6.57
C—Br	1.6	1.90	0.17	9.47
C—I	1.4	2.12	0.15	14.5
N—O	0.5	1.41	0.08	
N≡O	1.9	1.21	0.34	
C—C	—	1.52	—	1.21
(aliph)				
C=C	—	—	—	4.15
C≡C	—	1.19	—	6.02

\* For different value see Rep., 1936, 220. The values for *d* have been determined by various methods, namely X-ray examination, electron diffraction, &c.

volving certain assumptions including the following: (a) The value for the  $\overset{\leftarrow+}{\text{C}}\text{—H}$  link is 0.2, but it may have any value between 0 and 0.2; (b) the value for a given link is unaffected by other links in the same molecule: this may be approximately true except for aromatic compounds; (c) the valency angle is  $109.5^\circ$ , whereas in certain compounds with two and three covalencies, e.g.  $\text{H}_2\text{O}$ ,  $\text{NH}_3$ , the value may be  $90^\circ$ .

The following general conclusions can be drawn from the numbers given in the table:

1. In all cases H in the link  $\text{H—X}$  is + to X, and in the link  $\text{C—X}$  carbon is the + end, except with  $\text{C—H}$ . Generally an atom belonging to an earlier period forms the + member in any pair, and this is confirmed by wave mechanics.

2. The moments of both  $\text{H—X}$  and  $\text{C—X}$  increase as the atomic number of X increases within a *period*, e.g.  $\text{C—N} < \text{C—O} < \text{C—F}$ , and also as X decreases within any *group*, e.g.  $\text{H—As} < \text{H—P} < \text{H—N}$ ;  $\text{P—Br} < \text{P—Cl}$ . Exceptions are  $\text{C—O}$ , which is less than  $\text{C—S}$ , and  $\text{C—F}$ , which is less than  $\text{C—Cl}$ .

3. With multiple links the moment increases more rapidly than the number of links, cf.  $\text{C—N}$  and  $\text{C}\equiv\text{N}$ ,  $\text{C—O}$  and  $\text{C}=\text{O}$ ,  $\text{C—S}$  and  $\text{C}=\text{S}$ . A knowledge of the dipole moment of a link and of the distance between the two nuclei permits the calculation of the residual charges carried by each atom due to the unequal sharing of the linked electrons. The value is generally expressed as the fraction of the normal electron charge. Values are given in column 4 in the table.

### Bearings on Organic Structure

1. Compounds with co-ordinate links, as might be expected, have relatively high polar moments, e.g. sulfoxides and sulphones value 4–9, also additive compounds of  $\text{BCl}_3$ ,  $\text{AlCl}_3$ , with ethers, nitriles, and amines.

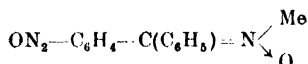
2. The observed increase in molecular polarization with concentration is explicable on the basis of molecular association due to the formation of co-ordinate links.

3. The power of H to act as an acceptor. Never with  $\text{C—H}$  link, rarely with  $\text{N—H}$ , but readily in  $\text{O—H}$  and  $\text{F—H}$ .

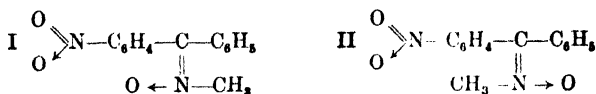
4. *Cis-* and *trans*-isomerism. The symmetrical *trans* com-

pound is non-polar, whereas the *cis* compound is distinctly polar. Hence in certain cases when only one form is known it is possible to determine its configuration from a determination of its dipole moment.

5. Oximes. The dipole moments of the two stereo-isomeric N ethers of *p*-nitrobenzophenone oxime

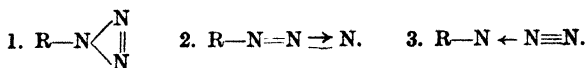


are as follows. The  $\alpha$ -methyl ether, m.-pt.  $159^\circ$ , has a moment 6.60, and the  $\beta$ -methyl ether, m.-pt.  $136^\circ$ , a value 1.09. The  $\alpha$ -compound with the high moment will obviously have the *syn* structure I as the two strongly polar groups  $\text{NO}_2$  and  $\text{NO}$  with co-ordinate links are close together, and hence augment each other, the  $\beta$ -compound with the low moment will have the *anti*-configuration II, where the  $\text{NO}_2$  and  $\text{NO}$  groups are on opposite sides of the molecule. As the  $\alpha$ -oxime corresponding with the  $\alpha$ -N-ether gives *p*-nitrobenzanilide by the *Beckmann* transformation and the  $\beta$ -oxime gives benzo-*p*-nitrilide under similar treatment, it follows that the OH of the oxime changes place with the hydrocarbon radicals on the opposite side of the CN group, as suggested by *Meisenheimer*, and not with the *syn* hydrocarbon radical, as suggested by *Hantzsch* (cf. Chap. L, C1) (*Taylor and Sutton*, J. C. S., 1931, 290):



The same authors have also used the study of the dipole moments of the O-ethers of  $\alpha$ - and  $\beta$ -*p*-nitrobenzaldoximes and O-ethers of  $\alpha$ - and  $\beta$ -*p*-nitrobenzophenone oximes (*ibid.* 1933, 63).

6. Azides.—There are three possible structures for azides:



The relatively low dipole moments of aromatic azides point to structure 1, as both 2 and 3 with co-ordinate links should have large moments. The volatilities and parachors support

this view, but X-ray examination of crystals of metallic azides shows the azide ion to have the rectilinear structure  $N \leftarrow N \rightarrow N$  or  $\bar{N} = \overset{+}{N} = \bar{N}$ .

**7. Diphenyl Derivatives.**—The fact that *pp'*-di-derivatives  $X \cdot C_6H_4 \cdot C_6H_4 \cdot X$  have practically the same moments as the *p*-compound  $X \cdot C_6H_4 \cdot X$  proves that *Kaufler's* formula, where the two rings form an angle with each other, cannot be correct, but that the rings lie in a plane.

**8. Benzene Derivatives.**—On the basis that benzene has a planar structure, *Thomson* (1923) has shown that the dipole moment of any disubstituted derivative,  $C_6H_4X_2$ , must have the following values, provided the moment of the link  $C-X = m$  is known, and assuming that the value of the angle between the  $C-X$  valencies is  $60^\circ$  in *ortho*,  $120^\circ$  in *meta*, and  $180^\circ$  in *para* compounds:

$$\text{For ortho: } \sqrt{m^2 + m^2 + 2m^2 \cos 60^\circ} = \sqrt{3}m.$$

$$\text{For meta: } \sqrt{m^2 + m^2 + 2m^2 \cos 120^\circ} = m.$$

$$\text{For para: } 0.$$

When the two substituents are different, say  $X$  and  $Y$ , and where the moment of  $C-X = m_1$  and  $C-Y = m_2$ , then the moments of the compounds  $C_6H_4XY$  are:

$$\text{ortho} = \sqrt{m_1^2 + m_2^2 + m_1 m_2}$$

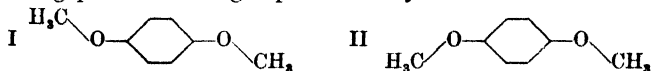
$$\text{meta} = \sqrt{m_1^2 + m_2^2 + m_1 m_2}$$

$$\text{para} = m_1 - m_2.$$

When the moments of  $C-X$  and  $C-Y$  have different directions, the same equations hold, but the signs must be taken into account.

The values of the moments of many disubstituted derivatives have been determined and compared with the values calculated as above. The values for the *o*-compounds are markedly 15 to 20 per cent lower than the calculated values where the two substituents have dipoles of similar sign. With *m*-compounds the two values agree within 10 per cent. With many *para* compounds the observed value for  $C_6H_4X_2$  is zero, but exceptions are met with in the case of a compound *p*- $C_6H_4(OMe)_2$ , where  $\mu = 1.74$ , and numerous other compounds containing O in the side chain, e.g. *p*- $C_6H_4(CHO)_2$ ,  $\mu = 2.35$ , *p*- $C_6H_4(CO_2Me)_2$ ,  $\mu = 2.3$ . With such compounds the resultant

moment does not lie in the central line of the molecule, the limiting positions being represented by



where the link  $-\text{OCH}_3$  is included in the nuclear plane. Compounds of the type  $p\text{-C}_6\text{H}_4(\text{NMe}_2)_2$  and  $p\text{-C}_6\text{H}_4(\text{CH}_2\text{Cl})_2$  also have definite moments.

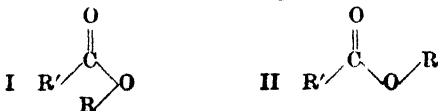
Free rotation of the groups  $\text{CH}_3\text{O}-$  or  $-\text{NMe}_2$  or  $-\text{CH}_2\text{Cl}$  about the link joining them to the nucleus may be assumed; it may also be assumed that the mean position of the groups lies much nearer to II, which is distinctly polar, than to I, which is non-polar.

9. Symmetrical tetrasubstituted methanes such as  $\text{CCl}_4$ ,  $\text{C}(\text{CH}_2\text{Cl})_4$ ,  $\text{C}(\text{CH}_2\text{Br})_4$ , and  $\text{C}(\text{CH}_2\text{I})_4$  have no moments and hence have perfectly symmetrical structures. Numerous analogous oxygen compounds, e.g.  $\text{C}(\text{OMe})_4 = 0.4$ ,  $\text{C}(\text{OEt})_4 = 1.1$ ,  $\text{C}(\text{CH}_2\text{OH})_4 = 2.0$ ,  $\text{C}(\text{CH}_2\text{Ac})_4 = 2.18$ ,  $\text{C}(\text{CH}_2\cdot\text{CO}_2\text{Me})_4 = 2.8$ ,  $\text{C}(\text{CH}_2\cdot\text{CO}_2\text{Et})_4 = 3.0$ , have distinct moments, the values being represented by the number given above. X-ray examination of the crystals of such substances supports the view that in these compounds the symmetrical structure is not maintained.

10. **Restricted Rotation.**—In compounds of the type  $\text{ClH}_2\text{C}-\text{CH}_2\text{Cl}$  it is concluded that free rotation about the  $\text{C}-\text{C}$  link is possible, as otherwise isomeric forms would be possible. In the vapour phase the chlorine atoms appear to be as far removed from one another as possible, as the moment is practically zero. At lower temperatures, however, a distinct dipole is present, and other positions of the chlorine atoms must be assumed, e.g. a partial restriction of the rotation has developed. The same phenomenon is observed with compounds such as  $\text{CH}_2(\text{CO}_2\text{Et})_2$ ,  $[\text{CH}_2]_8(\text{CO}_2\text{Et})_2$ , and  $[\text{CH}_2]_{16}(\text{CO}_2\text{Et})_2$ , which have  $\mu = 2.5$ .

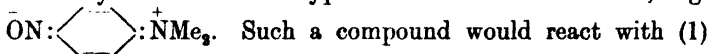
For acids and esters,  $\text{R}'-\text{C} \begin{smallmatrix} \text{O} \\ \parallel \\ \text{OR} \end{smallmatrix}$ , the dipole moments do not

vary in a given series. For saturated fatty acids the value is 1.4 and for esters 1.8. For the two possible extremes



the calculated values for  $\mu$  are 3.4 and 1.1. It appears that rotation is prevented, and the groups oscillate about a mean configuration of minimum potential energy corresponding roughly with II, and thus indicating a repulsion between R and R' and an attraction between O and R.

Compounds of the following types, *p*-nitraniline, *p*-nitroso-dialkylanilines, pyrones, thiopyrones, give anomalous dipole values, and *Sutton* (Trans. Far., 1934, 789) suggests that this may be due to a type of inner salt formation, e.g.



Such a compound would react with (1)  $\text{H}^+$ ,  $\text{OH}^-$  or (2)  $\text{CH}_3\text{I}$ , giving rise to (1)  $\text{OH}\cdot\text{NMe}_2:\text{C}_6\text{H}_4:\text{N}\cdot\text{OH} \rightarrow \text{OH}\cdot\text{C}_6\text{H}_4\cdot\text{NO}$ , and (2)  $\text{INMe}_2:\text{C}_6\text{H}_4:\text{NOMe}$ , and with benzoyl chloride would give  $\text{ClNMe}_2:\text{C}_6\text{H}_4:\text{N}\cdot\text{O}\cdot\text{COPh}$ .

It has been pointed out that the strength of an acid as measured by its dissociation constant varies with the type of substituents present (p. 193 and Chap. XXVI), and attempts have been made to correlate the dissociation constant with the polar characters of the substituent groups.

For the methane series the relationship can be expressed as  $\log k = \log k_0 - C(\mu + a\mu^2)$ , where  $k_0$  is the dissociation constant for acetic acid,  $k$  that for any other saturated fatty acid,  $C$  and  $a$  are constants, and  $\mu$  is the dipole moment of the acid. The change in strength of the acid is thus entirely due to dipole (inductive) effects of the substituent groups.

A similar generalization holds for *m*-substituted benzoic and phenylacetic acids, but with  $\text{NO}_2$ , Cl, Br, OMe in *ortho*- or *para*-positions the relationship is more complex (J. C. S., 1933, 893; 1934, 161, 1888; 1935, 343; J. Ind., 1935, 735).

For discussion of the effects of the solvent on the measurement of dipole moments see *Glasstone*, Rep., 1936, 117.

### Relative Polarizability of Bonds

The relative polarizability of covalent bonds depends primarily upon the relative mobility of electrons within the system, and is deduced from refractivities. Molecular refraction as determined by *Fajans* and *Knoor* (B., 1926, 256) and *Smyth* (Dielectric Constants and Molecular Structure, New York, 1931) have led to bond refractivities ( $P_{\text{B}}$ ), and as

these bear a linear relationship to bond polarizabilities they can be taken as measures of the latter. For values of  $P_E$  see column 5 in table (p. 1284). These values are practically of the same order as the reactivities, e.g. of the organic halides involving elimination of the halide ion.

## H. Molecular Volume, Parachor and Molecular Magnetic Rotation

The method adopted in all cases is to determine the molecular value for compounds of known composition and from these to calculate atomic values, namely, normal atomic volume, atomic parachor, and atomic magnetic rotation. At first it was thought that molecular volumes were purely additive, but later experimentation proved that constitution is also important, as the value for C varies according to the linking between the 2 carbon atoms, i.e. single, double, or triple bond, and the same holds good for O, S, and N attached to carbon.

### 1. MOLECULAR VOLUME

The mol. vol. is given by the expression mol. wt./sp. gr., and *Kopp* (1842) was the first to examine the mol. vols. of numerous compounds. The results showed that in a homologous series an increase of  $\text{CH}_2$  in composition corresponds to a fixed increase in the molecular volume, approximately 22, and as the at. vol. of carbon is twice that of hydrogen it follows that in many series of compounds the at. vol. of C = 11 and of H = 5.5. This holds good for paraffins, saturated alcohols, ethers, esters, &c. The value for oxygen depends upon its type of linking; for alcohols and ethers, i.e.  $\text{C}-\text{O}-\text{H}$  or  $\text{C}-\text{O}-\text{C}$ , the value is 7.8, but for carbonyl compounds, i.e.  $\text{C}=\text{O}$ , it is 12.2. Subsequently *Schiff* proved that the carbon value varies with the type of linking, i.e. single, double, or triple. The calculated value for the mol. vol. of ethyl formate,  $\text{H}\cdot\text{CO}\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_3$ , is  $3\text{C} = 33$ ,  $6\text{H} = 33$ ,  $1\text{O} = 12.2$ , and  $1\cdot\text{O} = 7.8$ , total 86.0 compared with the experimental value 85 to 86.

The method has not been used to any appreciable extent for determining the structure of organic compounds, as it suffers from the defect that the mol. vol. varies appreciably

with temperature. For further details, cf. *Thorpe*, J. C. S., 1880, 327; *Lossen*, A., 1883, 214, 138; *Horstmann*, B., 1885, 766; *Schiff*, A., 1884, 220, 71; also *Le Bas*, "Molecular Volumes of Liquid Compounds", London, 1915, and *Sugden* (J. C. S., 1927, 1780) for Molecular Volumes at Absolute Zero.

## 2. THE PARACHOR\*

This physical constant was introduced by *Sugden* in 1924 for the study of the structure of organic molecules. It is expressed by the equation  $P = \frac{M\gamma^{\frac{1}{3}}}{D - d}$ , where  $M$  = molecular weight and  $\gamma$ ,  $D$ , and  $d$  the surface tension, density of liquid and density of vapour at any temperature, or  $P = MC^{\frac{1}{3}}$ , where  $C$  = Macleod's constant and is equal to  $\gamma/(D - d)^{\frac{1}{3}}$  (J. C. S., 1924, 1185; 1929, 1055). The parachor = 0.77 mol. vol. at the critical temperature.

The parachor is an additive and also a constitutive property. Isomeric esters all have the same value, and the positions of the substituents do not affect the parachor of a di-substituted benzene derivative. Cis- and trans-stereoisomerides usually give the same value for  $P$ . In any given homologous series the increment  $\text{CH}_2$  corresponds with a rise of 39.6 in  $P$ .

The closing of a ring has an appreciable effect, greater with a small than a large ring, and unsaturation as represented by an olefine or acetylene linkage has a most marked effect, whereas conjugation of two olefine linkages produces the same effect as two such bonds farther removed in the molecule from one another. The double linking, whether C:C, C:O, C:S, C:N, or N:O, has the same value provided it is non-polar, and similarly the value for C:C and C:N is the same.

The following atomic and structural parachors have been determined by *Sugden* and others:

C = 4.8, H = 17.1, N = 12.5, P = 37.7, O = 20, S = 48.2, F = 25.7, Cl = 54.3, Br = 68.0, I = 91, triple non-polar bond = 42, double non-polar bond = 20, 3-membered ring = 14, 4-membered ring = 11.6, 5-membered ring = 9.5, 6-membered ring = 5.6, and 7-membered ring = 3,  $\text{O}_2$  in esters = 60.0, not 63.2 (i.e. two oxygens plus double bond or  $40 + 23.3$ ). (For a somewhat different set of values, see *Mumford* and *Phillips*, J. C. S., 1929, 2112; *Vogel*, 1934, 333.)

\* *Sugden*, "The Parachor and Valency", Routledge, 1930.

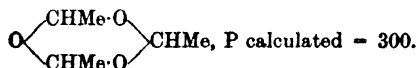


The parachor observed for benzene, viz. 206.2, is almost identical with that calculated for  $6C + 6H + 3$  olefine bonds + 6-membered ring, i.e. 207.1.

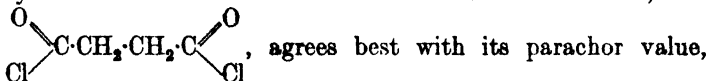
The following corrections must be used: all esters  $-2$ , OH group  $-5$ ,  $NH_2$ ,  $NHR$ , or  $NR_2$   $-2.5$ .

The lower value observed in the case of esters may be due to interaction between the two oxygen atoms and a reduction of unsaturation (cf. *Smedley*, J. C. S., 1909, 231).

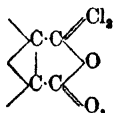
The parachor value has proved useful in the study of certain structural problems, e.g. paraldehyde (p. 152) might have either an open chain structure,  $OH \cdot CHMe \cdot CH_2 \cdot CH(OH) \cdot CH_2 \cdot CH : O$ ,  $P$  calculated = 317, or the cyclic structure



The value actually found, viz. 299, points to the ring formula. In the case of *p*-quinones (Chap. XXV, E.) the parachor value points to the ketonic and not the peroxide structure. The symmetrical structure for the chloride of succinic acid, viz.



and of the two phthalyl chlorides the one melting at  $15^\circ$  appears to be the symmetrical and the isomer melting at  $88.5^\circ$  the unsymmetrical,

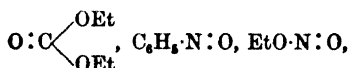


and thus confirms *Ott* and *Pfeiffer's* view (B., 1922, 413; cf. p. 535).

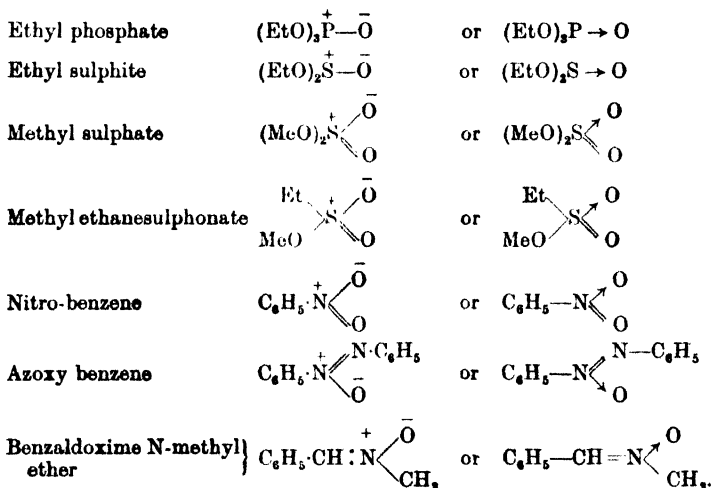
The values for benzil and similar  $\alpha$ -diketones agree with the usual ketonic formulæ rather than with cyclic systems, whereas the colourless isomeric forms sometimes isolated (B., 1922, 1174, 3753; *Irvine*, J. C. S., 1907, 541) are the cyclic or peroxide compounds. Chemically they are far less active.

The study of parachor values has proved most useful in the case of compounds containing double linkages between oxygen and sulphur or oxygen and nitrogen. The parachor values for alkyl carbonates, nitroso-compounds, alkyl nitrites and

sulphones as determined experimentally agree perfectly with the values calculated on the assumption that these compounds contain the non-polar double linking between C and O, N and O, S and O, i.e. the formulæ,



but with alkyl sulphites, alkyl sulphonates, alkyl sulphates, nitro compounds, azoxy compounds, and the N ethers of oximes the observed values for the parachor do not agree with the values calculated from the usual formulæ for these compounds, the observed values always point to a lower degree of unsaturation, i.e. fewer non-polar double linkages. These cases are readily explicable if the presence of a semi-polar double bond (p. 18) or co-ordinate link is assumed, as indicated in the formulæ:



Such formulæ are now generally accepted since:

1. The observed and theoretical values for the parachors agree within narrow limits.

2. They admit of most of the elements in the compound being represented with the stable outer octet of electrons, whereas ordinary dicovalencies give ten or more electrons in the outer sphere of some atoms.

3. They are in harmony with many stereochemical observations which are not explicable when ordinary dicovalency links are used (cf. amine oxides, alkyl sulphites, &c., disulphones, Chap. L, E.).

4. On this view a dipole is present in such systems, and this will tend to increase the dielectric constant and also association but to diminish volatility, and this is in agreement with what is known of the compounds.

The study of parachor values has proved of value in the case of azoinides. Both parachor values (B., 1928, 1529) and molecular refraction and dispersion values (*Philip*, J. C. S., 1908, 918; 1912, 1866) favour *Curtius'* cyclic formula (B., 1890, 3023) rather than the open chain formula II (*Thiele*, B., 1911, 2524):



### 3. MOLECULAR MAGNETIC ROTATION

The magnetic rotation is observed when a liquid or solution is examined in a strong magnetic field, e.g. between the poles of an electromagnet. It is quite distinct from the optical rotation observed with compounds with dissymmetric molecules (this Chap., I.).

Most of the observations have been made by *W. H. Perkin, Senior* (J. C. S., 1884–1902, and for new form of apparatus, cf. J. C. S., 1906, 608), who determined the molecular magnetic rotations of numerous series of compounds. The value is calculated from the formula  $\frac{M\alpha_1 d_1}{18\alpha_1 l d}$ , where  $M$  = mol. wt.,  $\alpha$  = observed rotation using a column of liquid  $l$  cm. long, and  $d$  = specific gravity of the liquid, 18 is the molecular weight of water,  $\alpha_1$  its observed rotation,  $d_1$  its density, and  $l_1$  the length of column used. It was not found possible to obtain definite atomic magnetic rotations for different elements and then to calculate the molecular rotations from these values as described under molecular volumes and parachor, but it was found possible to calculate the molecular magnetic rotation  $r$  of a compound from the equation

$$r = C + n \cdot 1.023,$$

where  $n$  represents the number of carbon atoms in the com-

pound, and  $C$  is a constant for a particular homologous series but differs from series to series.

A few of the constants are:

<i>n</i> -Paraffins ..	..	0.513	Higher esters ..	0.337
<i>iso</i> -Paraffins ..	..	0.631	Aldehydes ..	0.263
<i>n</i> -Alcohols ..	..	0.699	Alkyl chlorides ..	1.988
<i>iso</i> -Alcohols ..	..	0.844	Alkyl bromides ..	3.816
<i>n</i> -Fatty acids ..	..	0.391	Alkyl iodides ..	8.011
Alkyl acetates ..	..	0.370		

The molecular magnetic rotation of a complex compound can be calculated by taking as the series constant the mean of the series constants of the various groups of compounds which it represents. Thus ethyl lactate,  $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{C}_2\text{H}_5$ , possesses the groupings characteristic of an ethyl ester and also of a secondary alcohol; the series constants for these are:

Ethyl ester = 0.337; secondary alcohol = 0.844. Mean = 0.590.

The series constant for ethyl lactate and homologues is thus 0.590, and the molecular magnetic rotation of the lactate

$$5 \times 1.023 + 0.590 = 5.705,$$

which agrees very well with the experimental value, 5.720. The values of their molecular magnetic rotations have been used by *Perkin* in discussions on the constitutions of certain tautomeric compounds, especially those of the keto-enolic type, but the method is not one of those in general use for deciding structures.

Some general conclusions drawn by *Perkin* are:

(i) Monoketonic compounds and keto-esters, which react as tautomeric substances, as a rule, have the ketonic and not the enolic structure, except when a number of negative groups, such as phenyl and carboxethyl,  $\cdot\text{CO}_2\text{C}_2\text{H}_5$ , are present. These have an enolizing tendency, as shown in ethyl benzoyl-acetate,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}_2\text{C}_2\text{H}_5$ , which, according to *Perkin*, is a mixture of some 75 per cent of the keto- and 25 per cent enolic compound.

(ii) Acetylacetone at  $17^\circ$  consists of a mixture of some 80 per cent of the hydroxy-ketone,  $\text{CH}_3\cdot\text{CO}\cdot\text{CH}:\text{C}(\text{OH})\cdot\text{CH}_3$ , and some 20 per cent of the dienolic form,  $\text{CH}_3\cdot\text{C}(\text{OH})::\text{C}:\text{C}(\text{OH})\cdot\text{CH}_3$ . If alkyl radicals replace the hydrogen atoms of the methylene group of acetylacetone, the tendency to form

the enolic form is less marked, whereas the introduction of negative groups,  $\cdot\text{CO}_2\text{Et}$ , increases the tendency.

(iii) Rise of temperature favours ketonization.

#### 4. MOLECULAR REFRACTION

The molecular refraction, like the molecular volume, is to a large extent an additive property, i.e. the molecular refraction is the sum of the atomic refractions of the atoms present in the molecule, but it is to a certain extent constitutive; thus the oxygen atom has distinct atomic refractions according to whether it is in the carbonyl or oxide state of combination.

The refractive index itself,  $n = \frac{\text{sine of angle of incidence}}{\text{sine of angle of refraction}}$ , does not lend itself to the study of generalizations, but, according to *Gladstone and Dale* (1858), such generalizations are found when the specific refractory power,  $\frac{n-1}{d}$  (where  $d$  = specific gravity), is employed. This specific refraction varies but little with the temperature; thus with water:

$t$	0°	10°	20°	90°	100°
Specific refraction ..	0.3338	0.3338	0.3336	0.3321	0.3323,

and is not largely affected by the presence of other substances. A second formula for the specific refractive power has been introduced by *Lorentz and Lorenz*, viz.  $\frac{n^2-1}{(n^2+2)d}$ ; this has the advantage that the value appears to be independent of the physical state of the compound:

$t$	<i>Lorentz-Lorenz</i>		<i>Gladstone-Dale</i>	
	Gas	Liquid	Gas	Liquid
Water .. ..	10° 0.2068	0.2062	0.3101	0.3338
Carbon disulphide	10° 0.2898	0.2805	0.4347	0.4977
Chloroform ..	10° 0.1796	0.1790	0.2694	0.3000

When the refractive powers of different substances are compared, it is usual to employ the molecular refractive powers rather than the specific refractions. The molecular refraction is the product of the specific refraction into the molecular

weight; according to *Gladstone*  $\frac{M(n-1)}{d}$ , and according to *Lorentz-Lorenz*  $\frac{M(n^2-1)}{d(n^2+2)}$ .

The study of molecular refraction has proved of great value in the study of the structures of organic compounds. It is necessary to indicate the special light employed, e.g. the D sodium line or the  $\alpha$  hydrogen line, as the value varies with light of different wave-lengths.

*Landolt* examined the molecular refractions of the members of several homologous series, and came to the conclusion that the molecular refraction is an additive quantity, and that similar changes in composition induce similar changes in the molecular refractive power:

Alcohols				Acids			
		$M(n-1)$ $d$	Diff.			$M(n-1)$ $d$	Diff.
CH <sub>3</sub> ·OH ..	..	13·17	→ 7·53	H·CO <sub>2</sub> H ..	..	13·91	→ 7·20
C <sub>2</sub> H <sub>5</sub> ·OH ..	..	20·70	→ 7·60	CH <sub>3</sub> ·CO <sub>2</sub> H ..	..	21·11	→ 7·46
C <sub>3</sub> H <sub>7</sub> ·OH ..	..	28·30	→ 7·81	C <sub>2</sub> H <sub>5</sub> ·CO <sub>2</sub> H ..	..	28·57	→ 7·65
C <sub>4</sub> H <sub>9</sub> ·OH ..	..	36·11	→ 7·27	C <sub>3</sub> H <sub>7</sub> ·CO <sub>2</sub> H ..	..	36·22	→ 7·83
C <sub>6</sub> H <sub>11</sub> ·OH ..	..	43·38		C <sub>4</sub> H <sub>9</sub> ·CO <sub>2</sub> H ..	..	44·05	

and similarly for various groups of esters, the mean value for the CH<sub>2</sub> group being 7·6 units. By methods similar to those described under molecular volumes, values were obtained for the atomic refractive powers of the elements for the  $\alpha$  line, e.g. C = 5, H = 1·3, O = 3, Cl = 9·79, Br = 15·34, &c. The values thus obtained for the halogens are practically identical with those determined for the elements in the free state. The molecular refraction of any simple carbon compound can be calculated by adding together the atomic refractions of the constituent elements. Thus, for ethyl alcohol, C<sub>2</sub>H<sub>6</sub>O, the calculated molecular refraction is  $2 \times 5 + 6 \times 1·3 + 3 = 20·8$ , and that actually found experimentally is 20·7.

According to *Landolt*, the molecular refraction is purely additive, and thus isomeric compounds should possess identical molecular refractive powers. This is largely true in certain cases, e.g. the compounds C<sub>3</sub>H<sub>6</sub>O<sub>2</sub>—propionic acid, 28·57; methyl acetate, 29·36; and ethyl formate, 29·18.

In a series of investigations begun in 1878 (A., 1879, 200, 139; 1880, 203, 1 and 255) *Brühl* examined the influence of atomic grouping on the molecular refraction, and was able to show that the property is not purely additive, but to a certain extent constitutive. Thus a comparison of the experimental

and calculated values for unsaturated and the corresponding saturated compounds at once exhibits anomalies:

$\frac{M(n-1)}{d}$ for $\alpha$ -line.				
	Observed.	Calculated.	Difference.	
Allyl alcohol, $C_3H_6O$	.. 27.88	25.8	2.08	
Propyl alcohol, $C_3H_8O$	.. 28.60	28.4	0.2	

Similarly in other unsaturated compounds it is found that a double bond between two carbon atoms usually increases the molecular refraction by about two units (mean value 2.15), and a triple bond by 1.95 unit.

Other polyvalent elements have atomic refractions which vary with their state of combination; thus oxygen in carbonyl compounds has the value 3.4, but in hydroxy-derivatives and ethers the value 2.8. The following is a list of some of the more important atomic refractions used by *Gladstone*, by *Brühl* (L.-L. formula) and by *Auwers* (L.-L. formula for  $H\alpha$  line):

			<i>Gladstone.</i>	<i>Brühl</i>	<i>Auwers</i>
Carbon in saturated compounds	.. ..	..	5.0	2.365	2.413
Hydrogen	.. ..	..	1.3	1.103	1.092
Carbonyl oxygen in $\diagup C:O$	.. ..	..	3.4	2.328	2.109
Ether oxygen in $\diagup C-O-C \diagdown$	.. ..	..	2.8	1.655	1.639
Hydroxylic oxygen in $\diagup C-O-H$	.. ..	..	2.8	1.506	1.522
Chlorine	.. ..	..	9.9	6.014	5.933
Bromine	.. ..	..	15.3	8.863	8.803
Iodine	.. ..	..	24.5	13.808	13.757
Ethylene bond	.. ..	..	2.1	1.836	1.686
Acetylene bond	.. ..	..	1.95	2.22	2.328
Sulphur in $C:S$	.. ..	..	16.0	—	—
Sulphur in $C-S-H$	.. ..	..	14.1	—	7.63
Nitrogen in compounds $\diagup C-N \diagdown$	.. ..	..	—	2.76	2.807

*Brühl* has employed the molecular refraction for the investigation of certain tautomeric substances, e.g. ethyl acetoacetate. The observed value for the  $\alpha$ -line is 31.89, and the values calculated for the ketonic and enolic formulæ respectively, 31.53 and 32.55:

$\text{CH}_3\text{CO}\cdot\text{CH}_2\text{CO}\cdot\text{OC}_2\text{H}_5$		$\text{CH}_3\cdot\text{C}(\text{OH})\text{:CH}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$	
6C	= 14.190	6C	= 14.190
10H	= 11.03	1 ethylene bond	= 1.836
2O (carbonyl)	= 4.656	10H	= 11.03
1O (ether)	= 1.655	1O (carbonyl)	= 2.328
		1O (ether)	= 1.655
		1O (hydroxyl)	= 1.506
	<u>31.531</u>		<u>32.545</u>

The conclusion to be drawn from these numbers is that the ethyl acetoacetate at the ordinary temperature consists mainly of the ketonic form, but probably contains a small amount of the enolic. *Brühl* also tested the purity of numerous compounds prepared by him, by means of molecular refraction and dispersion determinations in place of ordinary combustions. *Perkin* and *Gladstone* have examined the molecular refractive powers of several di- and triketonic substances. For acetyl acetone at  $11^\circ$ , using the formula  $M(n-1)/d$  for the  $\alpha$ -line, the value 45.17 was obtained, and this decreased to 44.14 at  $99.3^\circ$ . The ketonic formula requires 42.2, the mono-enolic 43.7, and the di-enolic 45.2. At  $11^\circ$  the diketone undoubtedly consists mainly of the dihydroxylic compound  $\text{CH}_3\cdot\text{C}(\text{OH})\text{:C:C}(\text{OH})\cdot\text{CH}_3$ , and at the higher temperature, probably of a mixture of the mono- and dihydroxylic forms.

Later measurements by *Auwers* (B., 1911, 3530) for keto-enolic equilibrium mixtures show close agreement with the results obtained by *Meyer* (p. 873), and still later experiments (A., 1918, 415, 169, J. A. C. S., 1931, 1491) show that the examination of specific refractivities and dispersions can be used for differentiating between the keto and enolic forms of simple aldehydes and ketones, but is of no value in the case of  $\beta$ -di-ketones, as the mono-enolic form then contains a conjugate system of double bonds, which produces an abnormal increase in the refraction and still more in the dispersion.

Stereo-isomerides of the type of maleic and fumaric acids have not necessarily the same molecular refraction. Simple ring formation has but little effect on the molecular refraction; in the case of polymethylene compounds it produces an increment of from 0.5 to 0.7, and in discussions bearing on the structure of terpene hydrocarbons weight is attached to the values for molecular refraction, as it is frequently a choice



between a bicyclic formula with no double bond or a monocyclic formula with a double bond (B., 1900, 3124; 1907, 1120), the latter producing an increment of 2 units. This method has been used in the case of thujone and sabinene.

A hemicyclic double bond, i.e. an olefine linking between a carbon atom in the ring and one in the side chain (cf. terpinolene, p. 966, and  $\beta$ -phellandrene, p. 966), produces a greater exaltation than an olefine linking in the ring, e.g. an increase in  $M_D$  of 0.4. This generalization is of value in discussions on formulæ of terpene derivatives; for example, it agrees with the hemicyclic linking in camphene.

Conjugation of double bonds produces pronounced exaltation of molecular refractivity, and abnormally high values for  $M_D$  can frequently be used as an argument for the presence of such conjugate linkings in the compounds concerned, e.g. in the case of  $\alpha$ -terpinene (p. 965). The effects of conjugation are not simple, and are dealt with in Chap. LI, E.

*Auwers* and *Eisenlohr* (J. pr., 1910, 82, 70; Zeit. phys., 1910, 75, 585; 1912, 79, 129) have shown that similar relationships hold for specific and molecular dispersivity. The dispersivity is the difference between the refractivities for colours of different wave-lengths, e.g.:

$$r_\gamma - r_\alpha = \frac{n_\gamma^2 - 1}{(n_\gamma^2 + 2)d} - \frac{n_\alpha^2 - 1}{(n_\alpha^2 + 2)d}$$

$$\text{and } M_\gamma - M_\alpha = \left( \frac{n_\gamma^2 - 1}{n_\gamma^2 + 2} - \frac{n_\alpha^2 - 1}{n_\alpha^2 + 2} \right) \frac{m}{d}.$$

For comparative purposes these authors use the dispersivity values  $\times 100$  (sp. dispersivity) and find that it varies more markedly than refractivity with constitution.

*Auwers* and *Schmidt* (B., 1913, 457) show that normally the values for specific refractivity and dispersive power follow the order acid  $>$  chloride  $>$  ethyl ester. This also holds for many dibasic acids, and points to the symmetrical structure for succinyl and phthalyl chlorides (pp. 274, 535; also this chapter, section F. For discussion cf. *Lowry*, J. C. S., 1929, 2858).

## I. Optical Activity \*

Attention has already been drawn to the fact that compounds, the molecules of which are dissymmetric (Chap. L, A.) are, when in the liquid, dissolved or vapour phase, optically active, i.e. able to rotate the plane of polarization (pp. 90 and 179) either to the right (dextro-rotatory) or to the left (lævo-rotatory). The specific rotatory power  $[\alpha]$  of a liquid is obtained by dividing the observed rotation by the length of the column of liquid used and by the specific gravity of the liquid  $[\alpha] = \frac{\alpha}{l \times d}$ , and the molecular rotation is the product of the specific rotatory power into the molecular weight (M).

For a solution:

$$[\alpha] = \frac{100a}{l \times c} = \frac{100a}{l \times p \times d} = \frac{a \times v}{l \times g},$$

where  $c$  = concentration or number of grams of the active compound in 100 c.c. of solution,  $d$  = specific gravity of the solution,  $p$  = per cent of active substance in the solution, and  $g$  = number of grams of active substance in  $v$  c.c. of solution. The specific rotatory power of a solution may often be increased enormously by the introduction of an inorganic salt; some of the most effective are boric acid and alkali molybdates and tungstates. The nature of the monochromatic light, e.g. sodium light, is indicated, also the temperature and the nature of the solvent, e.g.  $[\alpha]_D^{15}$ , where  $D$  indicates that the number refers to sodium light and that the determination was made at  $15^\circ$ . Various attempts have been made to deduce general conclusions bearing upon the amount of rotation and the constitution of the compound. *Guye* (C. R., 110, 714) has attempted to connect the degree of asymmetry of the molecule of a compound  $C$   $a$ ,  $b$ ,  $c$ ,  $d$  with the masses of the four radicals present and the distance of the centre of gravity of the molecules from the centre of the tetrahedron (C. R., 1896, 1309; 1898, 181, 307). The researches of *P. F. Frankland* and others (J. C. S., 1899, 337, 347, 493, &c.) have shown that *Guye's* conclusions are not of general application.

*Patterson* and his co-workers (for summary see Trans. F. Soc., 1914, 10, 111, also J. C. S., 1914-39) have made a careful

\* "Optical Rotatory Power", *Lowry*, London, 1935.

investigation of the influence of solvent, temperature, &c., on the rotatory powers of various substances. He finds that *dilute* solutions of ethyl tartrate in water, or in methyl, ethyl or propyl alcohol, possess a higher specific rotation than the pure ester itself, that the specific rotation increases with dilution until a concentration of 10 gm. in 100 gm. of solvent is reached, and then the rotation remains practically constant. The highest values are always obtained with aqueous solutions, and the other solutions follow in the order—methyl, ethyl, *n*-propyl, isobutyl, and *sec*-octyl alcohol.

The values for nicotine in various solvents have much the same relationships as those of ethyl tartrate (*Winther*, *Z. physiol.*, 1917, **60**, 621).

The effect of increase of temperature upon corresponding solutions varies somewhat. In water the coefficient is negative for dilute solutions, but in the various alcoholic solutions it is positive, as it is also for the pure ester.

According to *Patterson* the change in specific rotation with solvent or temperature is not to be attributed to association but rather to the internal pressure of the solvents.

The different effects which two isomerides have on the rotation of ethyl tartrate, e.g. the *syn*- and *anti*-forms of an oxime, the true and *aci*-forms of  $\omega$ -nitrotoluene, and the keto and enolic forms of phenyl-formyl-acetic ester can be used for determining the velocity at which the one isomer becomes transformed into the other (*Patterson* and others, *J. C. S.*, 1907, 504; 1908, 1048; 1912, 27, 2100; 1929, 1895).

*Pickard* and *Kenyon* have determined the rotations of the different members of the series of carbinols, I,  $R\cdot CH(OH)Me$ , II,  $R\cdot CH(OH)Et$ , and III,  $R\cdot CH(OH)\cdot CHMe_2$ , and the esters,  $R\cdot CO\cdot OCHR'\cdot CH_3$  (*J. C. S.*, 1911, 45; 1912, 620, 1428; 1913, 1923; 1914, 830, 1115, 2226, 2262; 1915, 115; 1923, 1422), and draw the conclusion that there is no simple numerical relationship between the values for the members of any homologous series. In series I the rotation increases from ethyl to decyl without reaching a limiting value, but the propyl compound  $C_3H_7\cdot CHMe\cdot OH$  is abnormally high; in series II the maximum is reached at the amyl compound  $C_5H_{11}\cdot CHEt\cdot OH$  and in series III at the butyl compound  $C_4H_9\cdot CHPr^{iso}\cdot OH$ ; and with the esters  $Et\cdot CHR\cdot OAc$  and  $EtCH(C_6H_{13})\cdot O\cdot COR$  there is always a maximum when the total number of carbon atoms in the chain or the number of carbon atoms in *R* is 5

or 10 (*Kenyon*, *Trans. Far.*, 1930, 440). For effect of substituents in *o*-benzoic esters cf. *J. C. S.*, 1929, 2274, 2516.

Very interesting results bearing upon the relationships between optical rotation and structure have been obtained in the sugar group:

1. *Haworth* and *Hurst* (*J. C. S.*, 1928, 1221) have pointed out that in the equilibrium mixture ( $\alpha$ - and  $\beta$ -forms) of an aldose there is always a larger amount of the form which has the OH groups attached to C atoms numbered 1 and 2 in *trans*-positions, whether this be the  $\alpha$ - or the  $\beta$ -form. With *d*-glucose the amount is 66, with *d*-galactose 69, and with lyxose 75 per cent.

2. According to *Hudson* (*J. A. C. S.*, 1909, 66) the rotation due to carbon atom No. 1 in the case of many sugar compounds is affected in only a minor degree by changes in the structure of the remainder of the molecule:

$\alpha$ -Methyl- <i>d</i> -xyloside	}	Difference in $M_D = 359^\circ$	
$\beta$ - " "			
$\alpha$ -Methyl- <i>d</i> -glucose	}	" " = $375^\circ$	
$\beta$ - " "			
$\alpha$ -Methyl- <i>d</i> -gentibioside	}	" " = $361^\circ$	
$\beta$ - " "			

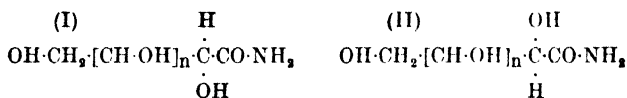
and also a change in the structure of carbon atom No. 1 affects in only a minor degree the rotation due to the remainder of the molecule.

$\alpha$ - and $\beta$ -Glucoses.	Sum of $M_D = 237$
$\alpha$ - and $\beta$ -Methylglucosides.	" = 242
$\alpha$ - and $\beta$ -Glycolglucosides.	" = 235

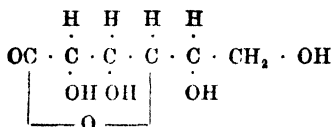
By this method *Hudson* predicted the molecular rotations of a large number of sugars then unknown, and these have been verified in 14 cases. Exceptions are known, and it is possible that a *cis*-OH group attached to an adjacent carbon atom has a disturbing effect (*Haworth* and *Hirst*, *J. C. S.*, 1930, 2616; also *Hudson*, *Rapport sur les Hydrates de Carbone*, Liege, 1931).

3. In the case of amides of the gluconic acid series, *Hudson* (*J. A. C. S.*, 1918, 813; *Maltby*, *J. C. S.*, 1922, 2608; 1923, 1404) finds that the spatial arrangements of the  $\alpha$ -carbon atom are the deciding factor in determining the nature of the

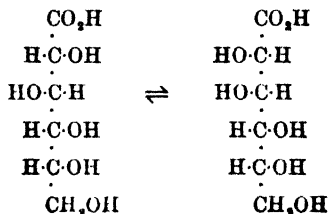
rotation. In all cases compounds in which the group can be represented as in I are *d*- and as in II *l*-rotatory.



4. For relationships between configuration of lactones of monobasic acids allied to the sugars and optical rotation see Chap. LVI, A1, and the same generalization holds good for 11 lactones of the dibasic acids (saccharic acids). A few exceptions are met with, e.g. *d*-erythronic acid, *d*-mannonic and *d*-allonic acid. A modified form of the rule is, all cyclic sugar derivatives which have the OH group attached to C atom No. 4 on the right of the projection will be dextro-rotatory provided that an OH attached to one of the other carbon atoms, viz. 2, 3 or 5, has the opposite configuration, whereas, if the OH groups at 2, 3, 4 and 5 all lie on the same side, the lactone will be feebly dextro- or even lævo-rotatory, and this is the structure of the three exceptions mentioned above, e.g. *d*-allonolactone:

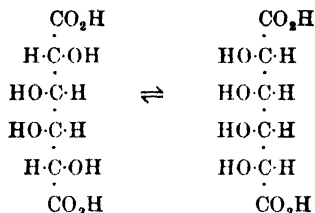


5. Attention has been drawn (p. 252) to the fact that *d*-gluconic acid when heated with pyridine or quinoline at 130° to 150° is transformed into an equilibrium mixture of *d*-gluconic and *d*-mannonic acids. A comparison of the configurations of the two acids indicates that the change—*d*-gluconic to *d*-mannonic acid—is due to epimerization at carbon atom No. 2:



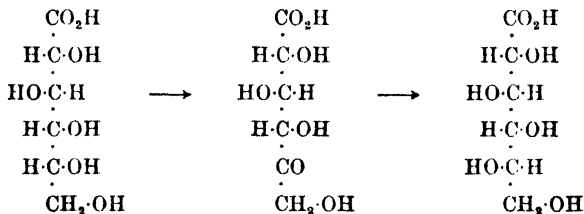
A similar relationship holds good for *d*-galactonic and *d*-talonic acids and for fully methylated lactone derivatives, and epimerization at carbon atom No. 2 appears to be a fairly general phenomenon.

Dibasic acids of the saccharic series can undergo epimerization at carbon No. 2 or carbon No. 5, e.g. ammonium mucate heated at 135° in aqueous solution is largely converted into *allo*-mucic acid:



The following changes also indicate epimerization at carbon atom No. 5.

Gluconic acid  $\xrightarrow{\text{conc. HNO}_3}$  5-ketogluconic acid  $\xrightarrow{\text{red}}$  two aldonic acids, viz. *l*-idonic acid and a stereoisomeride:



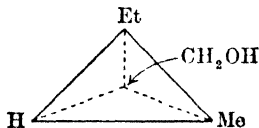
Numerous experiments have also been made on rotatory dispersion, and it has been found that *Biot's* generalization that the rotation varies inversely with the wave-length is by no means true, and cases of anomalous dispersion are common (*Patterson*, J. C. S., 1916, 109, 1139, 1176; *Tschugaeff*, Trans. F. Soc., 1914, 10, 28; *Lowry* and *Austin*, Bakerian Lecture, T. R. S., 1921).

## 1. ABSOLUTE CONFIGURATION

Various suggestions have been made as to which of the two spatial arrangements of an active compound has + and which - rotation, but the conclusions based on different suggestions do not always agree.

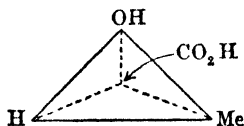
Boys (P. R. S., 1934, A., **144**, 655, 675) has calculated the optical rotatory power of simple dissymmetric compounds  $Cabcd$ , where  $a, b, c$  represent  $H, Me, Et$ , and  $d$  represent  $OH, \cdot CH_2 \cdot OH$  or  $\cdot CH_2 \cdot NH_2$ . If we assume that the molecule is that determined by the close packing of four spheres, corresponding with the four different groups, around the central atom, then the magnitude and the sense of the rotation is determined by the refractive centres in the molecule. The specific rotation is given by means of a formula in terms of (*a*) refractive index of the medium, (*b*) total refractivities of each group, (*c*) radii of the groups, (*d*) wave-length of light used, and (*e*) mol. wt. of the compound.

The method also gives the absolute configuration, e.g. *l*-amyl alcohol is



where  $H, Me, Et$  form the base of the tetrahedron and  $\cdot CH_2 \cdot OH$  the apex below the plane of the paper.

Using a different method, Kuhn (Z. phys., 1935, B., **31**, 23) concludes that the configuration of *d* (-) lactic acid is



## 2. MUTAROTATION

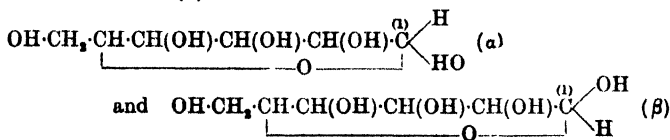
The change in rotation of an optically active solution is usually known as **mutarotation** (p. 350), and is a property exhibited by various optically active compounds, especially sugars, e.g. glucose, galactose, xylose, milk-sugar, and maltose, and certain hydroxy acids and their lactones, e.g. anhydrous lactic acid. In all these cases the rotation changes when the solution is kept; with glucose, for example, the value decreases to half, with milk-sugar the values are as 1.6:1, with galactose 1.46:1, and with xylose 4.67:1. The rotatory powers of maltose and lactic acid solutions increase when kept.

All acids and alkalis appear to facilitate the conversion, and

in the order of their degree of ionization. Common salt, alcohol, and various organic compounds, on the other hand, tend to retard the transformation.

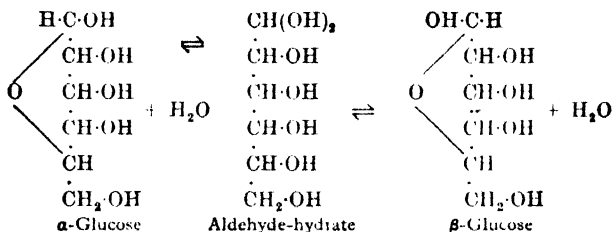
Various theories have been brought forward in order to account for the phenomenon. The first of these assumed the presence of complex molecules, e.g.  $(C_6H_{12}O_6)_x$ , in the freshly-prepared solution, and the gradual decomposition of these into the simpler molecules,  $C_6H_{12}O_6$ , thus producing a lowering of the rotatory power. The assumption of the presence of complex molecules was rendered untenable as soon as it was shown that the molecular weight, as determined by the cryoscopic method, is the same in the freshly-prepared and the old solution. The second explanation was that, after solution, water is either withdrawn from, or added to, the original molecular aggregates. The present view is that the different rotations are due to different isomeric substances present in the two solutions, and that a gradual change in rotation accompanies the conversion of the one isomeride into the other.

*Tanret* (1895) claimed to have isolated three distinct modifications of *d*-glucose, which had the respective specific rotatory powers  $\alpha = +105^\circ$ ,  $\beta = +52.5^\circ$ , and  $\gamma = +22.5^\circ$ . More recent work (*E. F. Armstrong*, J. C. S., 1903, 1305; 1904, 1043) indicates that in the case of *d*-glucose only two distinct isomerides actually exist in solution, viz. the  $\alpha$  and  $\gamma$ , and that the so-called  $\beta$ -modification is merely a mixture of the  $\alpha$  and  $\gamma$  in chemical equilibrium. The two modifications now termed  $\alpha$  and  $\beta$  and not  $\alpha$  and  $\gamma$  are represented as stereo-isomeric, and correspond in structure with the  $\alpha$ - and  $\beta$ -methyl-glucosides (p. 350 and Chap. LVI, F.), since these glucosides, when hydrolysed with enzymes, have rotatory powers of the order of those of the  $\alpha$ - and  $\beta$ -glucoses, and the addition of an alkali to the products of hydrolysis produces the same change as with the  $\alpha$ - and  $\beta$ -sugars. They are represented by the following configurations, the only difference between the two being the spatial arrangements of the radicals around the terminal C atom numbered (1):



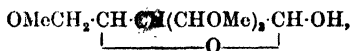


(Compare also *Behrend* and *Roth*, A., 1904, **331**, 359, and *Lowry*, J. C. S., 1904, 1551.) Both  $\alpha$ - and  $\beta$ -compounds can be isolated in a state of purity by crystallizing *d*-glucose from acetic acid, in the one case at the ordinary temperature and in the other hot (*Hudson* and *Dale*, J. A. C. S., 1917, 320). The  $\alpha$ -compound has  $\alpha_D + 111.2^\circ$ , and the  $\beta + 17.5$  (*ibid.* 1919, 559). *Lowry* concludes that in an ordinary solution of glucose, in addition to the  $\alpha$ - and  $\beta$ -modifications, small amounts of the aldehyde or aldehyde-hydrate are also present. This accounts for the aldehydic properties of glucose solutions, and also affords an explanation of the conversion of the  $\alpha$ - into the  $\beta$ -glucose:



*E. F. Armstrong* (J. C. S., 1903, 1305) suggests that the mutarotation proceeds through the addition of water to the oxygen atom of the ring, e.g.  $\begin{array}{c} \text{OH} \\ \diagup \\ \text{O} \\ \diagdown \\ \text{H} \end{array}$ , and *Irvine* and *Steele*

(1915, 1230) arrive at the same conclusion from a study of the electrical conductivity of aqueous solutions of tetramethyl- $\alpha$ -glucose. According to *Boeseken* (B., 1913, 2612; Rec. trav., 1915, **34**, 96, 272), a marked exaltation in the electrical conductivity of boric acid is produced by the addition of a carbon compound containing hydroxyl groups attached to adjacent atoms. When tetramethyl- $\alpha$ -glucose,



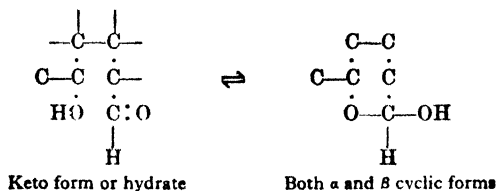
with only one OH group, is dissolved in dilute boric acid solution the conductivity of the system gradually rises to a maximum which persists when mutarotation is complete. This points to the addition of H and OH (i.e. water) to the ring O atom, adjacent to the  $\cdot\text{CH}\cdot\text{OH}$  group, and thus the equi-

brium is not between the simple  $\alpha$  and  $\beta$  sugars, but between the corresponding oxonium hydrates. By the aid of models it can be seen that by the elimination of water from the oxonium hydrate, and by the shifting of an atom of H from O to C, the conversion of the  $\alpha$  sugar into the  $\beta$  is possible. It is probable that the mutarotation of  $\alpha$ -glucose itself is therefore due to the formation of oxonium hydrates. Mutarotation can also occur in non-aqueous solvents, e.g. acetone or formamide (*McKenzie and Ghosh*, P. R. S. Edin., 1914, 35, 22), and it is probable that in these cases also the enolized solvent forms oxonium compounds with the ring O atom of the sugar. (For résumé, see *Lowry*, B. A. Rep., 1904, 193; *Irvine and Steele*, J. C. S., 1915, 1230.)

The following is a list of sugars which show mutarotation, with the optical rotation of the  $\alpha$  and  $\beta$  forms and of the equilibrium mixture:

	$\alpha$	Equil.	$\beta$
Glucose .. ..	111.2°	52.2°	19.2°
Galactose .. ..	144.5	81	52.2
Mannose .. ..	30	14.6	-14
Fructose .. ..	—	-93	-133
Sorbose .. ..	—	42.9	—
Xylose .. ..	92	19	—
<i>l</i> -Arabinose .. ..	175	105	55.4
<i>l</i> -Rhamnose .. ..	30.2	10.1	—
<i>l</i> -Fucose .. ..	—	-75.3	-93
Lactose .. ..	90	55.3	35
Maltose .. ..	—	136	118
Cellobiose .. ..	—	35	16

*Baker, Ingold, and Thorpe* (J. C. S., 1924, 705) point out that the mutarotation of sugars is to be attributed to a labile H atom and is a simple case of ring-chain tautomerism (Chap. LIII, B4).



It is now generally agreed that mutarotation of sugar derivatives is dependent on prototropic change, but there is difference of opinion as to the function of the catalyst in promoting the change (*Lowry* and others, *J. ph. Chem.*, 1929, **33**, 9; *Tran. Far.*, 1928, 683; *J. C. S.*, 1925, 1371, 1385, 2883; *P. R. S.*, 1928, 505; *Baker, J. C. S.*, 1928, 1583, 1979; 1929, 1205).

The study of mutarotation of the two series tetracetylglucosidylanilides and the corresponding tetramethyl compounds (i.e. the OH of the cyclic tetramethylated or tetraacetylated sugar replaced by  $\cdot\text{NHC}_6\text{H}_5$  or  $\text{NH}\cdot\text{C}_6\text{H}_4\text{X}$ , where X is OMe, Me, Br in *para* positions) by determining velocity coefficients has shown that the same sequence occurs as in the case of the dissociation constants of the compounds  $(p)\text{C}_6\text{H}_4\text{X}\cdot\text{NH}_2$  as bases, which supports the tautomeric conception of mutarotation.

The mutarotation curves of the simpler sugars, e.g. glucose and its derivatives, follow the unimolecular law within the limits of experimental error, whereas the coefficient for galactose rises from 0.064 to 0.0192 (equilibrium value).

Other compounds also show mutarotation, e.g.  $\alpha$ -nitrocamphor (p. 985) and bromo- $\alpha$ -nitrocamphor (*Lowry, J. C. S.*, 1899, 211).

Each of these compounds appears to exist in two distinct forms, one of which contains the nitro-group  $\text{>CH}\cdot\text{N}\begin{array}{c} \nearrow \text{O} \\ \searrow \text{O} \end{array}$ , and

the other the isonitro-group  $\text{>C:NO}\cdot\text{OH}$ . Ordinary crystalline nitrocamphor, melting at  $102^\circ$ , is regarded as consisting of the normal form, its homogeneity being vouched for by the constancy of its initial specific rotatory power ( $[\alpha]_D = -124^\circ$  in 5-per-cent benzene solution) and by its well-defined crystalline form. When dissolved the nitro-compound at once begins to change into the pseudo form, and this change is accompanied by an alteration in the rotatory power; with the 5-per-cent benzene solution the specific rotatory power has fallen to  $-104^\circ$  at the end of four days, and then remains stationary. This solution represents a mixture of the normal and pseudo-compounds in dynamic equilibrium, and assuming that the pseudo-compound, which so far has not been obtained in a pure form, has a specific rotatory power  $+180^\circ$  in benzene solution, then the solution with a rotation of  $-104^\circ$  contains some

93 per cent of the normal and 7 per cent of the pseudo form.

The velocity of the transformation, normal  $\rightarrow$  pseudo, is increased by rise of temperature, by increase in concentration, and by the addition of traces of alkalis.

The polarimetric method has also been used for measuring the velocity change of *l*-menthyl *d*-phenyl-acetoacetate,  $\text{CH}_3\cdot\text{CO}\cdot\text{CHPh}\cdot\text{CO}_2\cdot\text{C}_{10}\text{H}_{19}$ , into the enolic form,  $\text{CH}_3\cdot\text{C}(\text{OH})\cdot\text{CPh}\cdot\text{CO}_2\cdot\text{C}_{10}\text{H}_{19}$  (A., 1913, 398, 372).

Camphoric acid (Chap. LVII, C2) also shows mutarotation in the presence of concentrated hydrochloric acid, as *isocamphoric* acid is formed owing to the epimerization of the  $>\text{CH}\cdot\text{CO}_2\text{H}$  group, whereas the  $>\text{CMe}\cdot\text{CO}_2\text{H}$  retains its configuration.

Mutarotation of sugars and of nitrocamphor is catalysed by acids and still more by bases. In chloroform solution in glass vessels nitrocamphor readily shows mutarotation due to alkali derived from the glass, but the change is stopped after a time owing to the formation of  $\text{COCl}_2$  from the chloroform.

Water molecules, as distinct from the  $\text{H}^+$  and  $\text{OH}^-$  ions, act as catalysts, and with pure water the catalytic activity of the water molecules is 10 times as great as that of the  $\text{H}^+$  and  $\text{OH}^-$  ions present, as the concentration of these latter is so small. Other amphoteric solvents, i.e. substances which can both give and accept protons, can act as catalysts, e.g. a mixture of pyridine and cresol.

The following are the catalytic coefficients for the mutarotation of glucose solutions at  $20^\circ$ :

$[\text{HCl}]$  0.5,  $[\text{HAc}]$  0.0065,  $[\text{H}_2\text{O}]$  0.00026,  $[\text{OAc}^-]$  0.069,

$[\text{NH}_4^+]$  0.0012,  $[\text{H}^+]$  or  $[\text{OH}_3^+]$  0.36,  $[\text{OH}^-]$  8000.

The active esters of certain  $\beta$ -ketonic acids, e.g. *l*-menthyl acetoacetate and *l*-menthyl formylphenylacetate (*Lapworth*, J. C. S., 1902, 1491), *l*-menthyl *d*-phenylacetoacetate and *l*-menthyl benzoylphenylacetate (*Rupe* and *Lenzinger*, A., 1913, 398, 372), exhibit mutarotation; this may be due to keto-enolic change of the keto ester. The active esters of  $\alpha$ -ketonic acids also exhibit mutarotation (*McKenzie* and others, Bio. Z., 1929-32), e.g. the esters of *l*-menthol, *d*- or *l*-borneol, *d*- or *l*- $\beta$ -octanols with pyruvic benzoylformic, anisoylformic and  $\alpha$ -naphthoylformic acids. The change is shown in ethyl alcoholic solution, but not in solvents such as benzene, acetone,

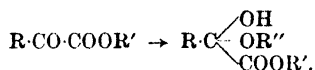
or chloroform, and the rate of change is increased by traces of acidic or basic catalysts, especially acidic, which in some cases produce an almost instantaneous equilibrium. From such alcoholic solutions by spontaneous evaporation of the solvent the ester is recovered with its *original* properties unchanged. All the pyruvates show decreased rotations on standing, whereas the other esters show increases.

Benzoin methyl ether,  $C_6H_5 \cdot CH(OMe) \cdot CO \cdot C_6H_5$ , has a different rotation in ethyl alcohol from what it has in inert solvents (*Wren*, J. C. S., 1909, 1585), and *l*-hydroxyhydrindamine and *d*-1 : 2-diphenyl-2-hydroxy-ethylamine,  $OH \cdot CHPh \cdot CHPh \cdot NH_2$  (*Read and Steele*, 1927, 910), show reversal of sign in ethyl alcoholic or acetone solution; cf. also *Wolfram* (J. A. C. S., 1930, 2464; 1931, 2275) for crystalline alcoholate of aldehydopentacetyl galactose.

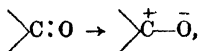
In some of these cases the mutarotation is due to formation of solvate complexes:

(a) Co-ordination complexes. The ester acts as a donor and the alcohol as acceptor. Other solvents, such as carbon tetrachloride and benzene, cannot act as acceptors. This does not explain why secondary and tertiary alcohols do not bring about mutarotation.

(b) Non-co-ordination complexes. Thus the carbonyl group can form an additive compound—semi-acetal—with the alcohol:

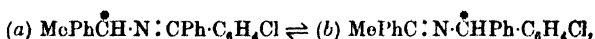


Another suggestion is that asymmetric induction occurs,



as in the case of sulphinic esters (Chap. L, E.).

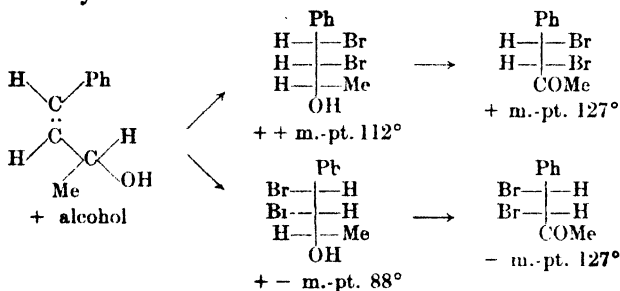
The study of the mesomeric change,



under the influence of sodium ethoxide, where a complex ion is the intermediate product, shows that if we start with an active compound (a) the product (b) is inactive. The rates of racemization and of mesomeric change as determined by distinct methods are practically the same; the conclusion, however, is drawn that optical activity persists in the inter-

mediate ions, but that these never become kinetically free (Ingold and Wilson, J. C. S., 1934, 93).

Kenyon and Partridge (J. C. S., 1936, 1313), starting with the two optically active  $\gamma$ -phenyl- $\alpha$ -methylallyl alcohols,  $\text{CHPh:CH}\cdot\text{CHMeOH}$ , by bromination obtained from each a pair of active dibromides: m.-pt.  $112^\circ$  with + rotation and m.-pt.  $88^\circ$  with - rotation from the +, and m.-pt.  $88^\circ$  with + rotation and m.-pt.  $112^\circ$  with - rotation from the other, and from these dibromides by oxidation two optically active dibromoketones were obtained,  $\text{CHPhBr}\cdot\text{CHBr}\cdot\text{COMe}$ , although the original centre of dissymmetry in the original alcohol had been destroyed:

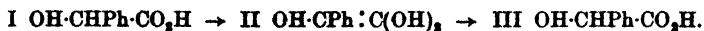


a reaction analogous to an asymmetric synthesis (this Chap., I5).

### 3. RACEMIZATION

Numerous optically active compounds lose their activity when heated or when kept in contact with acids or alkalis. This is due to the conversion of 50 per cent of the active form into its enantiomorph and is the simplest example of molecular rearrangement (Chap. XXXVIII).

The racemization of  $\alpha$ -hydroxycarboxylic acids is probably due to enolization:

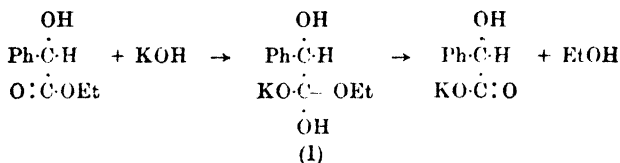


The active compound I undergoes enolization to II, whereby the dissymmetry of the molecule is destroyed, and on the change to III, where dissymmetry is again possible, equal amounts of *d*- and *l*-compounds will be formed. This view is supported by the fact that *l*-atrolactic acid,  $\text{OH}\cdot\text{CPhMe}\cdot\text{CO}_2\text{H}$ , which contains the carboxylic group attached to the asymmetric

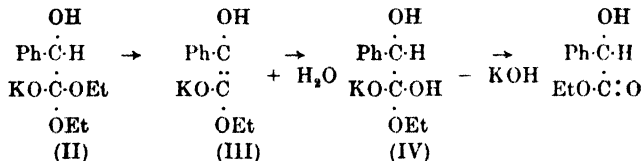
carbon atom but which cannot undergo tautomeric change owing to the absence of the necessary hydrogen atom, is remarkably stable and does not exhibit the phenomenon of racemization (see *McKenzie and Widdows*, J. C. S., 1915, 702).

Closely related to the above are the phenomena observed on hydrolysing the esters or amides of optically active acids with alkalis (*McKenzie and Wren*, J. C. S., 1919, 602; 1922, 1348). When aqueous sodium hydroxide is used, little or no racemization occurs, and the resulting acid is optically active; with alcoholic potash, which always contains a certain amount of potassium ethoxide, distinct racemization takes place, and if the saponification is incomplete, the unsaponified ester has undergone racemization to a greater extent than the acid formed.

In both cases the first stage in hydrolysis is probably an additive reaction at the carbonyl group: with aqueous potash KOH is the addendum, and with alcoholic potash KOEt. Thus with ethyl *l*-mandelate in aqueous solution the additive compound (I) immediately breaks up into the



*l*-potassium salt and ethyl alcohol; at no stage is the grouping around the asymmetric C atom disturbed. In alcoholic solution the additive compound (II) is optically active;



but by the elimination of alcohol gives an unsaturated inactive compound (III), which adds on water and loses KOH, yielding a mixture of equal amounts of *d* and *l* esters, as the reformation of the asymmetric C atom in (IV) is a synthesis from a compound previously devoid of one, and therefore results in the formation of equal amounts of optical antipodes.

The inactive ester in its turn is hydrolysed to inactive acid. The additive compound (IV) is identical with (I), except that it is the *d-l*-form, and the reason why it decomposes into KOH and ester rather than into potassium salt and alcohol is probably due to the presence of the large excess of alcohol which would prevent the dissociation in that particular direction.

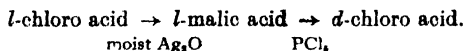
Ketones of the type  $\text{MePhCH}\cdot\text{CO}\cdot\text{Ph}$  are readily racemized in the presence of alkali, probably owing to enol formation (J. C. S., 1926, 779).

Traces of alcoholic potash added to *l*-menthyl *l*-phenylchloroacetate,  $\text{C}_6\text{H}_5\cdot\text{CHCl}\cdot\text{CO}\cdot\text{OC}_{10}\text{H}_{19}$ , produce racemization of the acyl (due to enolization) but not of the alkyl portion of the ester, and the result is a mixture of *l*-menthyl *d*-phenylchloroacetate (43 per cent) and *l*-menthyl *l*-phenylchloroacetate (57 per cent), and the same proportions are formed if *l*-menthyl *d*-phenylchloroacetate is the starting-point (B., 1923, 1962; 1924, 1582; 1925, 894; 1931, 1115).

The racemization shown by many optically active acids and bases derived from diphenyl (Chap. L, A5) is to be attributed to the rotation of the substituted phenyl groups about the common axis. This rotation can be hindered but not completely blocked by certain ortho substituents, e.g. 2:2'-disulphonic acid, or 2:2'-diiodo-4:4'-dicarboxylic acid.

#### 4. THE WALDEN INVERSION

A simple type of molecular rearrangement occurs during what is termed the *Walden* inversion, the first example of which was the conversion of *l*-chlorosuccinic acid into the *d*-acid by a simple series of reactions:



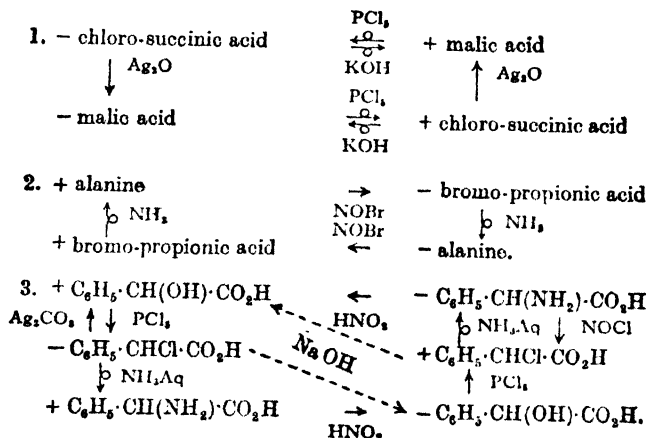
It is clear that in one of the two reactions a rearrangement of the groups around the central atom (centre of dissymmetry) must have occurred, but it is not easy to state at which, as the - malic acid may correspond in structure with the + chloro acid. Further investigations indicate that the inversion occurs at the second reaction, i.e. with  $\text{PCl}_5$ . The mere fact that in a chemical reaction the final product has a rotation of opposite sign to the initial substance does not necessarily mean a rearrangement around the centre of dissymmetry.



This is shown in the case of *l*(-) amyl alcohol and its acetate *l*(+) amyl acetate. Although both belong to the same series, *l*, the alcohol has a - and its acetate a + rotation (cf. this Chap., p. 1321).

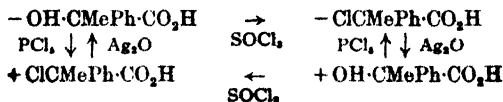
Walden (B., 1899, 1833), in a series of experiments on the reaction between *l*-chloro- and *l*-bromo-succinic acids and various alkalis, found that the hydroxides of potassium, rubidium, and ammonium gave practically pure *d*-malic acid, moist silver oxide gave the pure *l*-malic acid, and the hydroxides of sodium, barium, lead, and lithium gave mixtures in which the *d*-acid preponderated, whereas oxides of mercury and palladium gave mixtures in which the *l*-acid was in excess. The conclusion was drawn that the reaction with potassium hydroxide is normal, and that inversion occurs when silver oxide is used.

Examples of complete cycles are:

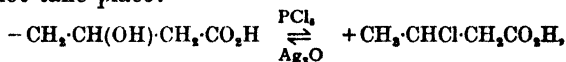


In the above reactions the  $\rightarrow$  indicates the point at which the inversion occurs.

It is not essential that the centre of dissymmetry should carry a hydrogen atom, as phenylmethylglycollic acid can undergo inversion (McKenzie and Clough, J. C. S., 1910, 1016):

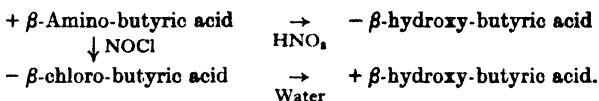


Practically all the inversions mentioned above occur when the asymmetric carbon atom has a carboxyl group attached to it. Experiments made by *E. Fischer* and *Scheibler*, with compounds in which the asymmetric atom is in the  $\beta$ -position with respect to the carboxylic group, indicate that inversion does not take place:

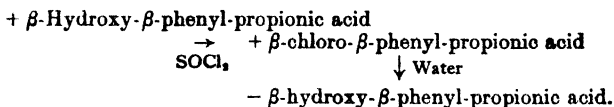


and similar results are obtained when the methyl esters are used. The same holds good in the case of  $\beta$ -hydroxy- $\beta$ -phenyl-propionic acid (*McKenzie* and *Humphreys*). There are, however, several exceptions, e.g.

1. *Fischer*:

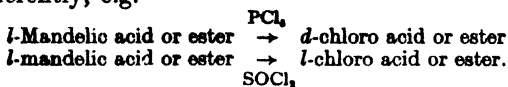


2. *McKenzie and Barrow*:

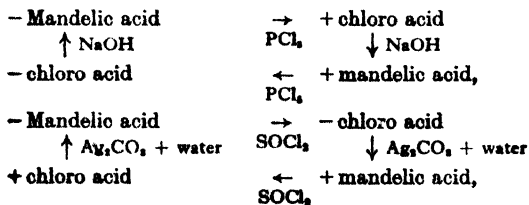


*Pickard* and *Kenyon* (1911, 45) and *McKenzie* and *Clough* (1913, 109) have shown that secondary alcohols devoid of both  $\cdot\text{CO}_2\text{H}$  and  $\cdot\text{CO}$  groups can undergo inversion, e.g.  $+\text{C}_6\text{H}_5\cdot\text{CHMeOH}$  with  $\text{SOCl}_2$  followed by either  $\text{Ag}_2\text{O}$  or  $\text{NaOH}$  yields the epimeride.

Frequently phosphorus pentachloride and thionyl chloride react differently, e.g.



In connexion with this the following cycles are of interest:



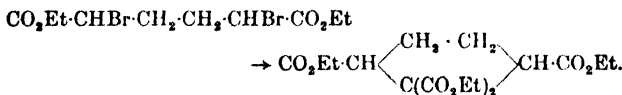
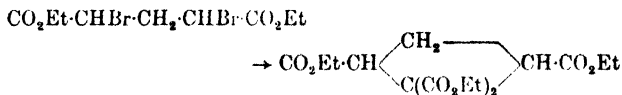
and generally the reaction with  $\text{SOCl}_2$  followed by  $\text{Ag}_2\text{CO}_3$  produces inversion, but whether this occurs in the first or second stage it is difficult to say. Impurities in thionyl chloride can bring about intramolecular change (M., 1913, 561; Bull. Soc., 1913, 13, 229).

Inversion also takes place in compounds containing no  $\text{COOH}$  or  $\text{COOR}$  group.

It does not follow that in all cases where inversion occurs the pure epimeride is formed, as much racemization can occur and the product will then be a mixture of the active compound with the racemic.

Senter and others (J. C. S., 1915, 638; 1916, 1091; 1918, 140, 151; 1924, 2137; 1925, 1847) have studied the effects of various solvents on the inversion in the case of ammonium phenylchloroacetate,  $\text{C}_6\text{H}_5\cdot\text{CHCl}\cdot\text{COONH}_4$ , when Cl is replaced by  $\text{NH}_2$ . They find that there is change of sign with 6 solvents, and no change with 6 others. The latter include water and benzonitrile, and the former liquid ammonia and acetonitrile. In the case of the replacement of Br by  $\text{NH}_2$  in  $\alpha$ -bromophenylpropionic acid there is always change of sign of rotation whichever solvent is used, and at the same time appreciable racemization. Replacement of OH by Br in  $\text{OH}\cdot\text{CHPh}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$  produces the same bromo acid in all solvents.

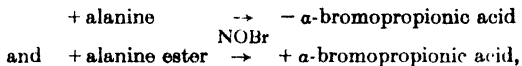
A change in configuration during ring closure has been observed by Perkin and others (J. C. S., 1921, 1393; 1924, 1492). Thus the esters of the  $\alpha\alpha'$ -dibromoglutaric and adipic acids exist in *meso* and *dl* forms, under the influence of sodio ethyl malonate ring closure takes place, and an ester of a tetracarboxylated cyclobutane or cyclopentane is formed:



If no inversion occurs the *meso* bromo derivative should yield the *meso* tetracarboxylic ester in both cases, and similarly the *dl* bromo-compound should yield the *dl* cyclic esters. In reality it is found that starting with either pure *meso* or

pure *d-l* bromo-compound the product is a mixture of *meso* and *d-l* cyclic esters.

**Detection of Inversion.**—Numerous attempts have been made to ascertain in which particular reactions inversion occurs, e.g. whether by NaOH or Ag<sub>2</sub>CO<sub>3</sub> or moist oxide in the replacement of halogen by OH, and whether by SOCl<sub>2</sub> or PCl<sub>5</sub> in replacement of OH by Cl. *Walden* argued that the reaction with strong alkalis which are largely ionized would probably be one of direct displacement, and hence not a case of inversion; the reaction with silver oxide would therefore be a case of inversion, and could be accounted for by the formation of an additive compound with the metallic hydroxide and subsequent removal of metallic chloride. *Fischer*, by comparing the reactions,



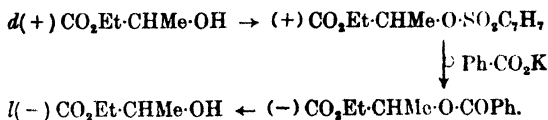
argued that inversion is less liable to occur with an ester than with an acid, and hence the first reaction represents an inversion. Subsequent experiments by *McKenzie* have shown that inversion can occur with esters, as ethyl  $\alpha$ -phenyl-lactate yields chloro esters of different signs when treated with PCl<sub>5</sub> or SOCl<sub>2</sub>. In 1913 *Frankland* (*J. C. S.*, 1913, 738) stated that "there does not exist at the present time any criterion whereby the relations between the configuration of an optically active compound and that of a derivative can be decisively ascertained".

*Freudenberg* (*B.*, 1914, 2037) claimed that the four hydroxy acids *l*-lactic, *l*-glyceric, *d*-malic, and *d*-tartaric all possess the same relative configurations, i.e. the H, OH, and CO<sub>2</sub>H radicals attached to the asymmetric carbon atom have similar spatial dispositions in all four compounds, since they can be transformed one into the other by reactions which do not involve displacements of groups directly attached to the asymmetric atom, and, so far, no case is known in which such a change causes inversion. Thus taking malic acid as the standard the four acids should be denoted as *d*(−) lactic acid, *d*(−) glyceric acid, *d*(+) malic acid, and *d*(+) tartaric acid. The letter *d* denotes the configuration compared with a parent compound and the sign within brackets denotes the sign of the actual rotation.

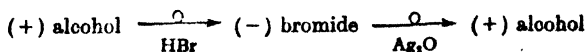
*Phillips* (J. C. S., 1923, 44) carried out the following series of reactions:

(+) Methylbenzylcarbinol,  $\text{CHMeBz}\cdot\text{OH}$ , with *p*-toluenesulphonyl chloride gives the toluenesulphonate (+)  $\text{CHMeBz}\cdot\text{O}\cdot\text{SO}_2\cdot\text{C}_7\text{H}_7$ , which with potassium acetate gives the acetate (-)  $\text{CHMeBz}\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ , and this on alkaline hydrolysis gives the carbinol (-). It is argued that the conversion into the sulphonate and also the hydrolysis of the acetate (p. 624) are reactions in which the bond between O and C is not broken, whereas the conversion of the sulphonate into the acetate involves the whole group  $\cdot\text{O}\cdot\text{SO}_2\cdot\text{C}_7\text{H}_7$ , as it is a reaction with the acetate ion  $\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ , and hence the inversion can only occur at this stage.

Similarly with the reactions in the formation of the benzoyl derivative of ethyl lactate (*ibid.* 1925, 399):



(+)  $\beta$ -Octanol can be converted into the (-) isomeride by a similar series of changes (*ibid.* 1929, 1700). The authors conclude that inversion invariably occurs when a group attached to an asymmetric C atom is replaced, unless a phenyl group is united to this atom or a carboxylic group is present in the molecule. Hence the common reaction,



involves two inversions.

*Clough* (*ibid.* 1918, 526; 1926, 1674) utilized the manner in which the rotatory power is affected by change of wavelength, solvent, concentration of solution, and addition of salts for elucidating the configurations of optically-active compounds, as compounds with a similar configuration are affected in the same manner by such changes in conditions. He drew a number of general conclusions relating to halogenated acids, hydroxy acids, and amino-acids, but the method is not of universal application.

*Boys* (P. R. S., 1934, A., 144, 655, 675) has described a method for determining the actual configuration of a simple

molecule, e.g. *l*-amyl alcohol, from a calculation of the effective radii of the groups H, Me, Et, CH<sub>2</sub>OH surrounding the asymmetric C atom, and has concluded that this alcohol has the configuration depicted in the diagram already shown on p. 1306 (end of section 1). It is further claimed that if one group is replaced without change of the configuration the sign of the rotation changes when the effective radius is increased above that of the next largest group. In the above compound if the OH is replaced by another group other than hydrogen the only one which can have a smaller radical volume is NH<sub>2</sub>; thus the amylamine with a configuration of the same type as *l*-amyl alcohol will also be *l*ævo rotatory. Any other radical X replacing OH produces a group ·CH<sub>2</sub>X with a larger volume than C<sub>2</sub>H<sub>5</sub> and hence will produce a change in rotation. Thus the compounds with ·CH<sub>2</sub>Cl, CH<sub>2</sub>OR, CH<sub>2</sub>·OAc will all be *dextro* rotatory although they belong to the *l*-series of *l*-amyl alcohol.

**Mechanism of Inversion.**—Several theories of inversion have been promulgated (*Fischer*, A., 1911, **381**, 132; *Werner*, B., 1911, 881; *Pfeiffer*, A., 1911, **383**, 123; *Gadamer*, C. Z., 1912, 1327; *Garner*, P. C. S., 1913, 198) but have not received general support. A view generally accepted is that inversion is due to a change of anions (*Lowry*, C. and I., 1924, 1128), e.g. the sulphonate (p. 1320) exchanges  $\bar{\text{O}}\cdot\text{SO}_2\cdot\text{C}_7\text{H}_7$  for  $\bar{\text{O}}\cdot\text{CO}\cdot\text{CH}_3$ . If complete separation of the sulphonate ion occurred the tetrahedral compound would be converted into a planar carbonium cation,  $\text{CHMeB}_2^+$ , and by the addition of the acetate ion a racemic mixture of the two isotopes would be formed. If, however, the acetate ion approaches the sulphonate molecule at the side away from the sulphonate group, then when exchange takes place—although the cation has no definite existence—the acetate ion takes up a position different from that occupied by the sulphonate group and inversion occurs. If, on the other hand, the acetate ion approaches the molecule on the same side as the sulphonate group, then direct replacement occurs and no inversion. Racemization occurs when the cation is formed even for only a very limited time, and partial racemization occurs when both replacement and addition to the cation occur.

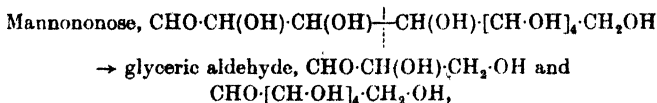
## 5. ASYMMETRIC SYNTHESIS \*

Most compounds with dissymmetric molecules obtained from natural sources are optically active and not racemic forms. The statement has been made that a compound derived from animal sources has always the same configuration, either *d* or *l*, e.g. *d*-glucose. In plant tissues sometimes only the one form is met with, e.g. *d*-fructose, *d*-glucose, *l*-malic acid, *l*-menthol. Other compounds occur naturally in all three forms, *d*, *l*, and *d-l*, e.g. *d*-borneol in the juice of *Dryobalanops camphora*, the *l*-form in *Blumea balsamifera*, and the *r*-form in Valerian oil.

A compound with a dissymmetric molecule prepared in the laboratory from symmetric compounds is invariably inactive, either a meso form or a racemic form, and an active form can be obtained only by the resolution of the latter.

Numerous attempts have been made to carry out an asymmetric synthesis, i.e. to obtain artificially an optically active compound from a symmetrical substance by the employment of an active product but without the use of an analytical process, e.g. such as those involved in the usual separation of racemic mixtures.

*E. Fischer* suggested the formation of the active mannononose from *d*-mannose by repeated cyanhydrin condensations, hydrolysis to the hydroxy acid lactone, and reduction to a sugar with one more carbon atom (Chap. XIV, A.). In each case only one new optically active hydrocarbon is obtained although two are theoretically possible. The second stage was the decomposition of this active mannononose into *d*-mannose and an optically active glyceraldehyde:



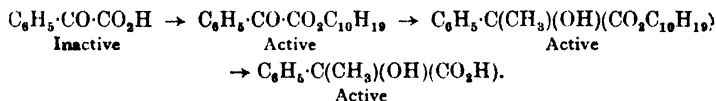
but unfortunately this reaction could not be realized.

*Cohen* and *Whiteley* (J. C. S., 1901, 1305), starting with cin-

\* "Asymmetric Syntheses—Asymmetric Induction", *P. D. Ritchie*, Oxford, 1933. *A. McKenzie*, C. and I., 1932, 491.

namic acid, prepared active amyl and menthyl esters, to which they added bromine and then attempted to obtain an active cinnamic acid dibromide,  $\text{C}_6\text{H}_5\cdot\text{CHBr}\cdot\text{CHBr}\cdot\text{CO}_2\text{H}$ , by the hydrolysis of the esters, but without success. The hydrolysis of the products obtained by reducing the active amyl and menthyl esters of mesaconic,  $\alpha$ -methylcinnamic, and pyruvic acids gave rise to inactive acids. Similar negative results were obtained by *Kipping* (P., 1900, 226).

*A. McKenzie* (J. C. S., 1904, 1250; 1905, 1373; 1906, 365) has succeeded in accomplishing several asymmetric syntheses. Thus when *l*-menthyl pyruvate,  $\text{CH}_3\cdot\text{CO}\cdot\text{CO}\cdot\text{OC}_{10}\text{H}_{19}$ , is reduced by aluminium amalgam, a mixture of unequal amounts of *l*-menthyl *d*-lactate and *l*-menthyl *l*-lactate is formed. When this mixture is hydrolysed by an excess of alcoholic potassium hydroxide and the *l*-menthol removed, a dextro-rotatory potassium salt containing an excess of *l*-lactate over *d*-lactate is produced; this mixture, when acidified, becomes lævo-rotatory, and the asymmetric synthesis of *l*-lactic acid is thus accomplished. If *l*-menthyl benzoylformate,  $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CO}_2\cdot\text{C}_{10}\text{H}_{19}$ , is treated in exactly the same manner, the final product is *r*-mandelic acid, due, probably, to the racemizing effect of the alkali. A second asymmetric synthesis has been accomplished by *McKenzie* by means of *Grignard's* reaction. Thus *l*-menthyl benzoylformate and magnesium methyl iodide yield the additive compound  $\text{CMePh}(\text{O}\cdot\text{MgI})(\text{CO}_2\text{C}_{10}\text{H}_{19})$ , which is converted by dilute acids into the *l*-menthyl phenylmethylglycollate  $\text{CMePh}(\text{OH})(\text{CO}_2\text{C}_{10}\text{H}_{19})$ , from which, on hydrolysis with alcoholic potassium hydroxide, a lævo-rotatory potassium phenylmethylglycollate,  $\text{CMePh}(\text{OH})(\text{CO}_2\text{K})$ , was obtained. Thus:

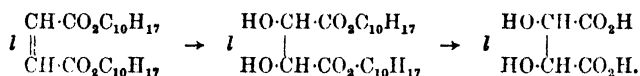


Similar active acids have been obtained by using other *Grignard* reagents in conjunction with *l*-menthyl benzoylformate. For numerous negative results, see J. C. S., 1922, 351. See also *Marckwald*, B., 1904, 349.

Another asymmetric synthesis (J. C. S., 1907, 1215) can be accomplished by oxidizing *l*-menthyl fumarate with dilute

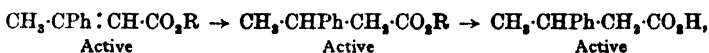


permanganate and acid and hydrolysing the dihydroxy ester formed when *l*-tartaric acid is obtained:



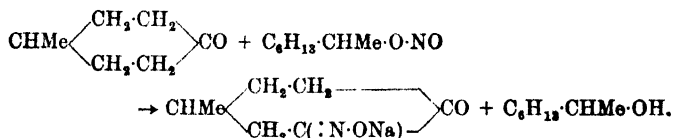
The monobornyl fumarate can also be used.

A similar synthesis is the formation of an active  $\beta$ -phenylbutyric acid by the catalytic reduction of esters of  $\beta$ -methylcinnamic acid derived from optically active alcohols (borneol, menthol, &c.) and subsequent hydrolysis (C. R., 1933, 196, 1614):



where R represents optically active alkyl group.

Another type is the formation of optically active cyclic oximes from inactive cyclic ketones and active *d* $\beta$ -octyl nitrite (Chap. L, C3) in the presence of sodium ethoxide:



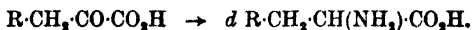
In all the above-mentioned cases the product is a mixture of *d*- and *l*-isomerides with one preponderating; in no case is a pure *d*- or *l*-compound formed.

*Bredig* and others (Bio. Z., 1912, 46, 7; 1932, 249, 244; 250, 414) have succeeded in preparing optically active hydroxy acids of the mandelic acid type by addition of HCN to an inactive aldehyde in the presence of an optically active base, e.g. *d*-quinidine, and hydrolysing the resulting cyanhydrin.

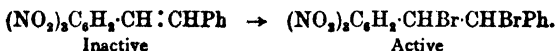
In the presence of *l*-chloro-amino-diethylenediamine-cobalt bromide,  $[\text{Co en}_2\text{NH}_3\text{Cl}]\text{Br}_2$  (Chap. XLVI, B.), certain racemic acids undergo differential oxidation, e.g. with *dl*-3:4-dihydroxyphenylalanine the *l*-amino acid is destroyed first.

In the synthesis of active mandelic acids it has been proved that certain enzymes, often in the form of plant extracts or tissues, can act in much the same manner as the active bases mentioned above. By using an extract of peach leaves with a low  $p_{\text{H}}$  value and low temperature an almost pure *d*-mandelo-

nitrile is formed (J. A. C. S., 1921, 164). Animal enzymes can also be used; thus  $\alpha$ -ketonic acids with ammonia in the presence of liver yield active  $\alpha$ -amino acids:



Numerous attempts have been made to bring about an *absolute asymmetric synthesis*, i.e. the synthesis of an optically active compound from an inactive one without the presence of another active compound but in an asymmetric medium (Boyd, 1896; Pirak, 1922), e.g. *d*- and *l*-circularly polarized light, but very few positive results have been obtained under controlled laboratory conditions. Davis and Heggie (J. A. C. S., 1935, 377) by the addition of bromine to 2:4:6-trinitrostilbene in *d*-circularly polarized light claim to have obtained a product with a very low rotation:



On the other hand, the asymmetric photochemical decomposition of several externally compensated compounds has been demonstrated. Thus Kuhn and Braun (1929) obtained a fairly active compound of unknown structure by the photochemical decomposition of *dl*-ethyl  $\alpha$ -bromo-propionate in circularly polarized light. Mitchell (J. C. S., 1930, 1829) effected the asymmetric photochemical decomposition of humulene nitrosate,  $C_{15}H_{24}N_2O_3$ , in the same manner.

Erlenmeyer, Jun. (1911) introduced the term *asymmetric induction*. He claimed that unsaturated compounds, particularly cinnamic acid or benzaldehyde, when treated with an optically active compound such as tartaric acid, either in solution or in the fused state, gave an optically active cinnamic acid or benzaldehyde after all traces of tartaric acid had been removed; but the results have not been confirmed by others. McKenzie (J. C. S., 1915, 444; 1922, 349) by treating aqueous solutions of potassium racemate with *l*-malic acid (1 mol.) obtained a crop of crystals consisting of a mixture of the acid potassium salts of *d*-tartaric and racemic acid. Of 15 different optically active acids used malic acid alone had this effect.

## J. Electrical Conductivity

Attention has previously (p. 185) been drawn to the fact that the degree of ionization,  $\alpha$ , of an acid in solutions of given concentration,  $v$ , may be determined by a comparison of the electrical conductivity,  $\lambda$  (reciprocal of resistance), at that dilution with the conductivity at infinite dilution when ionization would be complete, i.e.  $\alpha = \frac{\lambda}{\lambda_{\infty}}$ . From Ostwald's dilution

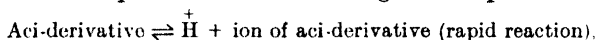
law, based on the law of mass action, it follows that  $\frac{\alpha^2}{v(1-\alpha)}$

is a constant  $= K$ , where  $v$  = number of litres of solution containing one equivalent of acid. This constant is known as the **dissociation constant**, and is used as a measure of the strength of all feeble acids. The effect of structure of the acid upon this constant has been discussed in Chap. XXXV.

*Hantzsch* has used the electrical conductivity method in the diagnosis of pseudo-acids and bases. Thus with certain nitro-compounds the ordinary compound  $R \cdot CH_2 \cdot NO_2$  is a pseudo acid and the isonitro-compound  $R \cdot CH : NO \cdot OH$  is a true acid, and all the salts are derived from the latter (p. 425). These salts, as a rule, are but little hydrolysed, as the isonitro-compounds are relatively strong acids. A solution of such a salt will thus

contain the metallic ions and the isonitro-ion  $R \cdot CH : NO \cdot O^-$ . When this solution is mixed with an equivalent quantity of hydrochloric acid the ions present are  $Na^+$ ,  $Cl^-$ ,  $R \cdot CH : NO \cdot O^-$  and  $H^+$ . In the majority of cases there is a considerable tendency for the strongly acidic and hence strongly ionized isonitro-compound (true acid) to become transformed into the ordinary nitro-compound (pseudo acid). As this is practically a non-electrolyte, it follows that as this transformation occurs the conductivity of the solution will gradually diminish until it attains the value of a sodium chloride solution of the given concentration. Thus with sodium *p*-bromophenylnitromethane,  $C_6H_4Br \cdot CH : NO \cdot ONa$ , at  $25^\circ$ , and  $v = 256$ , after mixing with an equivalent of hydrochloric acid, the conductivity  $\mu = 151.4$  after 1.5 minute, and after 45 minutes a constant value  $\mu = 129.5$ , was obtained. This approximates to the value  $\mu_{256} = 114.4$  for sodium chloride, and the difference may be due to secondary changes.

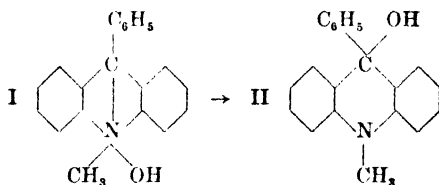
This reaction has been studied in detail by *Branch and Jaxon-Deelman* (J. A. C. S., 1927, 1765) in methyl alcoholic solution. After an initial disturbance due to the rapid formation of a comparatively weak electrolyte in equilibrium with its ions, one of these ions becomes involved in a slow unimolecular change resulting ultimately in the complete production of the pseudo acid. The changes are represented:



the negative ion then changes slowly into the ion of the pseudo acid, and this reaction is practically non-reversible, and finally the ion of the pseudo acid unites with a hydrogen ion rapidly by means of a covalency yielding the unionized pseudo acid.

For optically active nitro compound and sodium salt of isonitro compound, see *Kuhn and Albrecht*, B., 1927, 1297.

Similar results have been obtained with pseudo bases. The true base, methyl-phenyl-acridonium hydroxide (I), which is first liberated when salts of the base are decomposed with alkali, is readily transformed into the pseudo base with the carbinol formula (II):

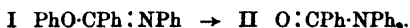


which is practically a non-electrolyte. When a solution of the chloride of the base is neutralized with an equivalent of sodium hydroxide, the solution has a maximum conductivity which gradually diminishes until the value for a solution of sodium chloride of the given concentration is practically reached. Similarly with the sulphate and an equivalent quantity of barium hydroxide; at  $0^\circ$  and  $v = 256$ , the initial conductivity was  $\mu = 119.2$ , but after 15 hours it had fallen to  $\mu = 1.7$  (due to small amounts of dissolved barium sulphate). Phenomena of this kind, which are termed by *Hantzsch* "slow neutralization", are largely used to denote tautomeric change, i.e. the change from a true acid to a pseudo acid or from a true base to a pseudo base (cf. pararosanine, p. 558; cotarnine, p. 1008)

during the conversion of the salt into the acid or base. Cf. *Madelung*, J. pr., 1925 [II], 111, 100; 1926, 114, 1; 1927, 115, 24.

For thionium pseudo bases, see *Hartley and Smiles*, J. C. S., 1926, 1821; 1927, 534.

Conductivity measurements have also been used in the study of the molecular rearrangement of N-phenylbenzimidazole phenyl ether I into benzoyldiphenylamine II by heating to 270°–300°:



The rearrangement can occur by dissociation of I into two radicals or two ions and their recombination to form II. Conductivity measurements favour the ionic view, as at 200° the molten mass has a very low conductivity, which rises rapidly with the temperature and finally becomes constant at the value corresponding to the pure compound II (J. C. S., 1925, 1992; 1927, 1740).

The effect of structure on other physical properties has been studied, e.g. **Internal Viscosity, Tesla Luminescence Spectra, Capillary Constants.**

## LXXII. UNIMOLECULAR FILMS \*

Mono-layers of large molecules are often formed at interfaces, e.g. water and air, mercury and air. In order to form stable surface films the molecule must contain a strongly polar group, e.g. carboxyl, to give the necessary adhesion to the surface, and a long non-polar hydrocarbon chain to prevent dissolution in the water—as a rule a chain of at least 14 carbon atoms. The amount of material necessary to form such a film is extremely small, e.g. 1 mg. or less. According to *Langmuir* (1933), the organic compound forms a liquid layer with both an upper and a lower surface tension. The upper is comparable with that between paraffin in bulk and air, and the latter with that between paraffin oil and water containing a few fatty

\* See *Adam*, "The Physics and Chemistry of Surfaces", Oxford, 1938. *E. K. Rideal*, "An Introduction to Surface Chemistry". Chem. Rev., 1941. 385.

acid molecules. With the aid of these films it has been found possible to study such processes as oxidation, hydrolysis, and polymerization, and also to determine molecular structure.

The maximum amount of a fatty acid that can spread on a given aqueous surface is limited by the number of molecules which can be packed into a single layer. With acids containing 16-30 atoms of carbon the cross-section of the molecule is constant, i.e. the same number of molecules constitute the mono-layer, but the length of the molecule increases with the number of carbon atoms. For stearic acid, length = diam.  $\times$  5, and for myricyl alcohol, length = diam.  $\times$  8.

The presence of olefine links in an acid increases the area per molecule, but the unsaturated compound is much more readily compressible. Triolein has an area three times that of tristearin, and castor oil has a still greater area.

The area per molecule occupied by stearic acid is 20.4 sq. Å. This represents a cross-section of the hydrocarbon chain when packed tightly together at an angle of about 23°. The area is the same as that found for crystals of stearic acid by X-ray analysis.

Acids spread on acidulated water (0.01N HCl) give much larger areas, e.g. 50 sq. Å, but these layers are much more compressible.

*Hughes and Rideal* (P. R. S., 1933, A., 140, 233) find that the oxidation of an unsaturated acid with the olefine link about the middle of the hydrocarbon chain, e.g. oleic acid, in a film on water containing permanganate takes place 10 times as rapidly under low compression, i.e. when the molecules are nearly flat, as when the film is highly compressed and the double link has less chance of reaching the water.

An examination of monolayers of di-substituted acetic acids  $R', CHRR'-CO_2H$ , shows that there is a tendency to expand, particularly when R and R' contain an appreciable number of carbon atoms, and the effect increases as the  $CO_2H$  group passes from the end to the middle of the molecules, i.e. is at its maximum when  $R = R'$ . Increase in the total number of carbon atoms in the acid has a condensing effect at low surface pressures and also at high pressures provided the smaller radical contains less than four carbon atoms. If this radical contains more carbon atoms, expansion occurs under high compression. (*Stenhagen*, Trans. Far. 1940, 597. For monolayers of long-chain alkyl sulphates,  $R \cdot O \cdot \dot{S}O_3$ , cf. *ibid.* 496.)

By the halogenation of *p*-hexadecyl-phenol,  $C_{16}H_{33}\cdot C_6H_4\cdot OH$ , with aqueous solutions of halogens *Alexander* (J. C. S., 1938, 729) has shown by a study of mono-films on suitable substrates and making use of surface pressure and surface potential measurements that the active intermediates are:  $HOI > HOBr > HOCl$  and  $\bar{I}_3 < \bar{Br}_3 < \bar{Cl}_3$ , and that  $HOI$  is 1000 times as active as  $\bar{I}_3$ ,  $HOBr$  0.25 times as active as  $\bar{Br}_3$  and  $HOCl$  only 0.001 times as active as  $\bar{Cl}_3$ .

The sterols and steroids generally form stable unimolecular films; as a rule the water soluble constituent is at one end of the molecule and the long side chain (at 17 diag., Chap. LXII, A.) at the opposite end of a four-ring skeleton, and in most of these cases the molecules stand upright. With coprostanone (cholesterol with the  $CH\cdot OH$  oxidized to  $CO$ ) the molecules are much tilted and the area covered is increased by about 50 per cent.

Surface film measurements have been used in determining the constitution of certain compounds, e.g. batyl alcohol, which is an ether of glycerol with one molecule of octadecyl alcohol. This gives a film closely resembling that of  $\alpha$ -monopalmitin, and hence has the long chain attached to an  $\alpha$ -oxygen atom and not to the central ( $\beta$ ) oxygen of glycerol.

When a highly polished chromium-plated block is dipped into a unimolecular film of stearic acid or its barium salt, a single layer of molecules is deposited on the metal and re-dipping results in the deposition of double molecular layers. When "Resoglaz" is used in place of the metal block, double layers are formed even at the first dipping.

In the single layers the hydrocarbon chains are closely packed and arranged irregularly, and the axes of the chains are practically normal to the surface. With an odd number of layers the first is irregular, but the upper layers regular as on "Resoglaz". With the acid the regularity results in crystals with monoclinic symmetry and with the barium salt in crystals with hexagonal symmetry. With "Resoglaz" it is the paraffin end of the chain which makes contact (J. Chem. Phys., 1938, 280). For reactions with mono-layers, cf. Nature, 1939, 144, 100.

## LXXIII. RESONANCE OR MESOMERISM \*

The following constants have been determined by different physical methods for the more common types of linkings in organic compounds: (a) length of link, (b) heat of formation, (c) resistance to deformation, (d) electrostatic disturbances.

The length of a link is not appreciably affected by the presence of other elements, and there is only a difference of some 10 per cent between single, double, and triple links in carbon compounds. According to *Eyring* and *Polanyi*, the extra energy required to bring about most reactions—energy of activation—is mainly devoted to stretching the links so as to bring the atoms into the positions required for the production of the new molecule, and the consequent rearrangement of the electronic orbits takes place relatively easily. It follows that the change from one form to another will occur the more rapidly the less the difference in the positions of the atoms in the two molecules. If this difference is very small the change will take place at once, and it will be impossible to isolate the less stable form.

A covalent link consists in the union of two atoms by means of a pair of electrons shared between the atoms. The one electron has a positive spin and the other a negative, and the influence of these electrons on the two nuclei is of primary importance; yet, according to wave mechanics, each electron affects every other electron and nucleus in the molecule, and such secondary effects influence the reactivities of certain atoms within the molecule.

The principles of resonance due to *Hund* and extended by *Pauling* to organic compounds are based on wave mechanics.

The equations of wave mechanics show that if a molecule can be represented, on the ordinary structural theory, by two different formulæ, then, under certain conditions, its actual state is neither of the two nor yet a mixture of the two in chemical equilibrium as in the case of many tautomeric compounds, but is a hybrid structure intermediate between the two—a resonance formula. This cannot be represented

\* *Ingold*, *Nature*, 1934, 133, 946; *Pauling and Wilson*, *Introduction to Quantum Mechanics*, New York, 1935; *Pauling*, Chap. 22 in *Gilman's Organic Chemistry*, 1938; *R. C. Evans*, *C. and I.*, 1940, 518, 560.



by the ordinary symbols, and it has to some extent the properties of both.

The two tautomeric forms are represented by two distinct *structural* or atomic configurations, e.g. differing by the position of a labile hydrogen atom (cf. Chap. LIII). The two resonance or mesomeric forms on the other hand often have the atoms in the same relative positions but possess different electronic configurations.

The conditions which must be satisfied for resonance to be possible are: (1) The positions of the atoms in the two structures must be approximately the same; the actual positions in the hybrid will be between the two and so involve a certain amount of strain with respect to either, but this must not be large. (2) The stabilities of the two forms must not differ greatly. The state of the hybrid is not necessarily half-way between the two forms; it lies nearer to the more stable one.

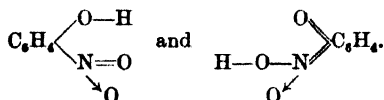
The presence of resonance has two important physical effects: (i) The energy content of the molecule is smaller (or its stability greater) than that of either form. This is of fundamental importance, as it follows that resonance must occur whenever it is possible under conditions 1 and 2 above. Hence the heat of formation is larger than that calculated for either of the two separate forms. Thus for the two forms of carbonic anhydride (p. 1334) the theoretical heats of formation are 348 and 350 K. cal. and the experimental value 380. (ii) The linked atoms in the resonance form come rather nearer together than in either of the two forms—owing to the greater strength of the link. For carbonic anhydride, formula I, the atomic distance is 2.48 and the actual distance is 2.26.

For the ketoenolic form of diketones two structures I and II are possible and are very similar. The resonance form is intermediate between the two and may be regarded as a form in



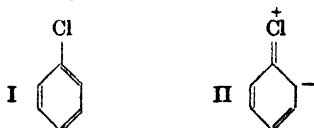
which the hydrogen atom is chelated between the two oxygens. The same holds good for *o*-aldehydophenols, but not for the saturated hydroxyketones,  $\text{R}\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CO}\cdot\text{R}'$ . For other examples, cf. *Hunter*, C. and I., 1941, 35. *Buravoy*, *ibid.* 1940, 855.

Another example is *o*-nitrophenol, where the two forms are:



Probably the same holds good for carboxylic acids, but two molecules are involved, as is indicated by the formation of acid salts from monobasic acids.

Resonance is also met with in chlorobenzene. One structure is represented by I, but there is a tendency for an electron to drift from its normal position, i.e. from the chlorine into the

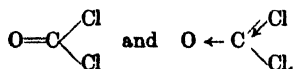


ring. If this drift were complete the product would be represented by II, and the resonance formula would be somewhere intermediate between the two. Support for such a structure has been given by *Sutton* (P. R. S., 1931, 133, 668) from a study of dipole moments. In reality *five* resonance configurations are possible, viz. the two Kekulé formulæ of I, two Kekulé formulæ of II and one form with the electron para to the chlorine.

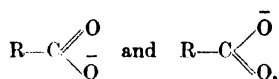
In carbon tetrachloride the length of the link X—Cl as determined by electron diffraction measurements is normal, whereas in the compounds  $\text{SiCl}_4$ ,  $\text{GeCl}_4$ ,  $\text{SnCl}_4$  the observed values for the X—Cl are always less than the normal—an indication of resonance, probably between the forms



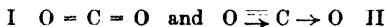
With  $\text{CCl}_4$  the second form is not possible, as the carbon atom cannot carry more than 8 electrons. Resonance, however, appears in the compounds  $\text{COCl}_2$  and  $\text{SOCl}_2$ :



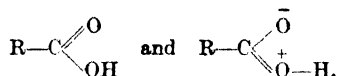
Relative simple cases of resonance are met with in the cases of the carboxylate ion, the nitro-group and in benzene. In the carboxylate ion the two forms are equal:



and the resonance formula in this case will be exactly midway between the two, neither oxygen will be attached to carbon by a complete double bond, the molecule will be symmetric, and the electron will be shared equally between the two oxygen atoms. With carbonic anhydride the resonance formulæ are:



With a carboxylic acid the resonance is more complex as the two forms are not equal:



The nitro group is similar to the carboxylate ion and the two oxygen atoms are symmetrically attached to nitrogen.

In the case of benzene all the C atoms are equivalent; the bonds between neighbouring C atoms are alike and intermediate between C—C and C≡C, namely 1.39 Å, and the general stability of the molecule is greater than would be expected if three double bonds were present. The resonance is between the two possible *Kekulé* formulæ and the *Dewar* formula, and the molecule is stabilized to the extent of 39 kilo calories.

For naphthalene the resonance formula approximates to the symmetrical structure (p. 568), but the unsymmetrical structure also contributes and the molecule is stabilized to the extent of 74 kilo calories. This energy of stability is termed **resonance energy**.

Electron diffraction measurements and also X-ray examination indicate a linear and not a cyclic structure for methyl azide, and probably a resonance formula between  $\text{—N}=\text{N}^+=\text{N}^-$  and  $\text{—N}^+=\text{N}^-\equiv\text{N}$ . Cf. p. 1280.

Similarly, diazomethane has not a ring structure but a linear resonance formula between  $\text{CH}_2=\text{N}^+=\text{N}^-$  and  $\text{CH}_2^+=\text{N}^-\equiv\text{N}$ .

Compare also *Helv.*, 1937, 400–513, for dyes, and *Trans. Far.*, 1935, 1491; 1937, 381, for urea derivatives.

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